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AN INTERNATIONAL JOURNAL REPORTING THE PRACTICAL APPLICATION OF OUR NEWER KNOWLEDGE OF NUTRITION

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The Journal of Clinical Nutrition

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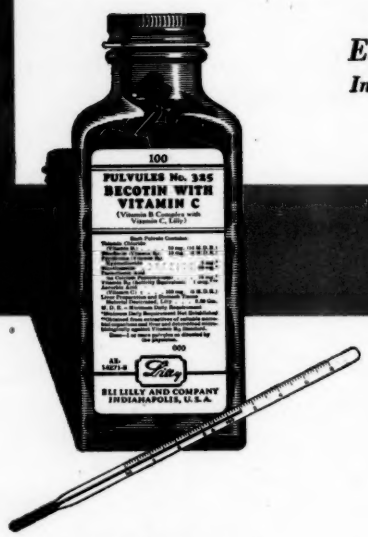

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THE JOURNAL OF CLINICAL NUTRITION

VOLUME 1, NUMBER 4 MAY–JUNE, 1953

Some Aspects of THE TONGUE *in* PELLAGROUS GLOSSITIS

By WILLIAM B. BEAN, M.D., AND MARGARET VANCE, M.D.

THE COMPLEXITY of clinical nutrition is well demonstrated in the problem of lingual disorders in deficiency diseases. Controversy over the significance of glossitis, its varieties, their causes and cures, has highlighted a polemical section of medical literature in which the present stage of relative quiet indicates confusion rather than solution. Fifteen years ago I (W.B.B.) began to make observations of the tongue in pellagra, using hand lenses, 20-power magnifiers, and later the slit lamp, in an effort to learn more of the minute morphologic changes in the tongue and the response to specific treatment. I was surprised when others who had observed the method outlined an elaborate group of categories with different significance, especially since many of the changes could be produced at will in the normal tongue by varying the temperature, moisture, exposure to air, pressure with a glass slide, smoking, and the application of mild irritants. To add to the confusion, the inherent subjectivity of the examination is influenced by the past experience and training of the observer, his attitudes and scientific dogmas, as well as the inborn variation in perceptive power.[1]

The purpose of this paper is to outline the usual characteristics of acute pellagrous glossitis, to review the necessary controls when glossitis is used as a gauge of the effectiveness of treatment, and to report the results of a number of therapeutic measures. If the observations fail to clarify our confusion, at least they define the problem in terms of the new work necessary for progress.

The patients who served as the subjects of these observations were admitted to the Medical Service of the University Hospital. While we have seen but one example of florid pellagra during four years in Iowa, pellagrous glossitis is seen occasionally in alcohol addicts or persons whose nutrition is disorganized by disease, and in a rare victim of whimsical eating habits. Dermatitis has been rare, as were diarrhea and the mental aberrations of pellagra.

Specific compounds were tested for possible therapeutic effect upon pellagrous glossitis as follows. The patient was hospitalized, confined to bed, and usually given a diet low in protein and vitamin B complex factors, or nothing but water and glucose for a three-day control period. The first patient will demonstrate the necessity for such a period of control before trial with any test substance. Several patients were kept in a metabolism ward, where rigid control of diet and activity were easier to enforce than in the open wards.

Though the evaluation was clinical in emphasis, we did such laboratory tests of vitamin levels and excretion as we were equipped to do. The results did not correlate well with the clinical state or its changes, and in an individual case did not throw light on the severity of depletion as estimated from the history and

From the Department of Medicine of the College of Medicine of the State University of Iowa and the University Hospitals.

Supported in part by the Medical Department Trust Fund and a grant from Eli Lilly and Company. Some of the equipment was supplied by the Subcommittee on Liver Disease of the U. S. Army Infectious Disease Commission.

the degree of glossitis. The discrepancy between laboratory results and clinical observations is a challenge for further study in both areas.

Symptoms of soreness, burning, bad taste, anorexia, feeling of illness or well-being were recorded, but our chief emphasis was on color photography. We were fortunate in having Mr. Frederick W. Kent and Mr. Richard A. Kent, of the Photographic Laboratory, as enthusiastic helpers in this part of the study. No efforts were spared to have lighting and other factors constant so that the pictures could be compared readily.

The paucity of clinical material, a tribute to prosperity which none would begrudge, makes the problem of evaluation difficult, since such investigations should have the respectability possible only with ample numbers for statistical validation. Our method was to let each patient serve as his own control, and make general comparisons. The data are presented as examples which need validation by further and extensive study. Brief case notes are given in the Appendix.

Results

The first example of change in pellagrous glossitis is found in Patient 1, who was given the control diet and kept in bed. This reduced her activity and calorie requirement, but at the same time restricted her source of vitamins. Even though her diarrhea continued, there was a slow but definite improvement in glossitis, so that after three days there was little trace of edema or the bright red color of the tip and margins (Figs. 1A and 1B). Had any putative curative agent been employed, it might well have received credit.

Patient 2, a woman with a partial resection of colon and ileum and fecal fistula, was put to bed and given the low vitamin diet for three days. There was no improvement in signs or symptoms. We then gave 25 mg. of cozymase intravenously, and within an hour she remarked that her tongue was no longer sore. By the end of 12 hours the tongue looked much improved and the redness and edema were subsiding, though a nearly normal state was not reached until 24 hours (Figs. 2A and 2B).

Patient 3 was not given a control diet but was observed for two days, during which she vomited every time she forced herself to try to eat. We gave her 100 mg. of cozymase and observed a decided improvement in sense of well-being. The tongue improved remarkably and 24 hours after the injection of cozymase it had lost the red-magenta color, but it was still smooth and appeared to have true papillary atrophy rather than just edema as the cause of the smooth, shimmering surface (Figs. 3A and 3B). Over the next nine days, in spite of an ample diet and vitamin supplements, the patient's tongue gradually became worse and appeared almost exactly as it had when she first entered the hospital. We decided that ACTH might affect the tongue adversely or favorably; and it was appropriate therapy for the arthritis. By the third day of ACTH injections (25 mg. every 6 hours) the tongue had become nearly normal (Fig. 3C) and the papillae could be seen. The patient felt much better, though she did not notice any qualitative difference from the lift she got after cozymase was injected. With ACTH, the feeling of health persisted longer. Her appetite improved but her food intake did not increase until after the tongue looked and felt better.

Patient 4, a 31-year-old farmer addicted to alcohol and poor food habits, was observed with signs of cirrhosis of the liver and pellagrous glossitis. After three days on the control diet he was given tryptophane in 9 doses of 100 mg. each at hourly intervals. Within 24 hours of beginning this treatment the tongue had become nearly normal in color but still had some edema, which was gone by the next day. There was very little change in subjective manifestations, though his tongue did feel better.

Discussion

These observations must be taken as suggestions for more extended work, rather than as established and final, since they were made on so few patients. The problem of control in experimental human nutrition is beset with difficulty and bounded by uncertainty.[2] Ignorance of the possibility of "spontaneous" improvement in acute pellagra when a patient is

Fig. 1A. (Patient 1). Early glossitis and cheilosis. The tip and margins of the tongue are bright red and a small amount of edema has ironed out the papillae, making the surface smooth.

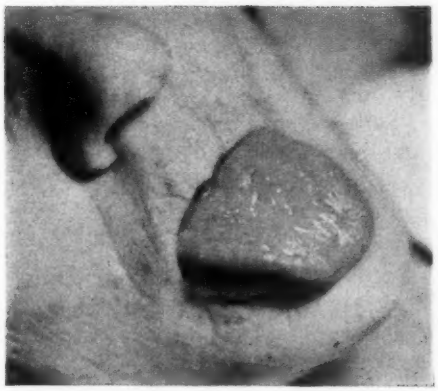

Fig. 1B. Tongue three days later during a period of rest in bed and use of a diet deficient in B complex vitamins. The color is normal and the edema of tip and edges has disappeared, leaving normal looking papillae.

Fig. 2A. Acute pellagrous glossitis. This photograph was taken at the end of the three day control period during which there had been no improvement. The tongue was sore, and very red at the tip, with some edema and smoothness.

Fig. 2B. Twenty-four hours after an injection of 25 mg. of cozymase. The tongue was no longer bright red at the tip and was not spontaneously painful or tender.

Fig. 3A. Acute and chronic glossitis with erythema and magenta color and true papillary atrophy as well as edema.

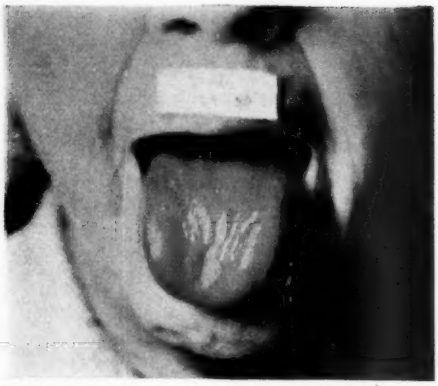

Fig. 3B. Return to a normal color 24 hours after an intravenous injection of 100 mg. of cozymase. Though the edema had gone, papillary atrophy was evident.

Fig. 3C. The tongue three days after ACTH therapy had been started at a time when the tongue had returned to the appearance in 3A. By now the papillae have returned and the color and texture are nearly normal though there is a slight magenta tint.

Figure A

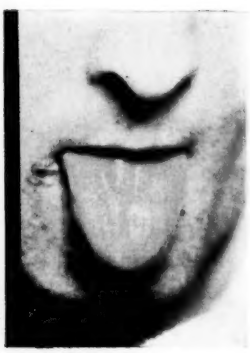

Figure B

Figs. 4A and B. The response of acute pellagrous glossitis after 900 mg. of tryptophane. Color returned to normal, edema cleared and the tongue was no longer sensitive to mildly irritating food or drink.

hospitalized and put to bed probably accounts for the host of forgotten specifics of the early decades of this century. Spies' demonstration of improvement occurring during a regimen of hospitalization and confinement to bed during which the pellagrins ate a "pellagra-producing" diet,[3] though very perplexing at the time, is the classic study of this phenomenon. Since we do not have detailed data on energy expenditure, tryptophane and nicotinic acid metabolism, we can only speculate on the reasons for this improvement. Perhaps rest reduces the need for respiratory enzyme precursors during the catabolic state of rest in bed, or actual cell destruction may liberate enough enzymes or vitamins to restore the delicate balance between supply and demand. Whatever the mechanism, the fact that improvement may occur even though food and vitamin intake is reduced or nil is warning of the necessity for a control period of waiting before any therapeutic agent is tested. If the depletion is severe, relapse follows shortly after this riptide of improvement and may be a tidal wave of disaster unless vitamins and a rich and ample diet are provided. The control period is one of potential danger and should not be tried by those inexperienced in clinical nutrition.

It was natural to try cozymase for therapeutic effect, since it contains nicotinic acid amide, which is assumed to be essential because it is a necessary building block whose synthesis the body cannot manage. More than a decade ago, with Spies and R. W. Vilter, one of us (W.B.B.) gave cozymase to pellagrins in relapse and noted improvement.[4] These observations, interrupted by the dislocations of World War II, have been continued in this clinic.[5] Patients 2 and 3 are examples of the very rapid improvement in glossitis after intravenous injection of cozymase. Within a few minutes after the injection was completed each patient volunteered the information that the burning and soreness in the tongue had diminished. Since cozymase produces an effect much like adenylic acid when given intravenously,[6] it is disagreeable and potentially dangerous. Electrocardiographic abnormalities, chiefly rhythm disturbances, occur often but are brief. After the reaction there may be an increased sense of well-being which seems to be more than the relief that an unpleasant experience is over. The improvement in the tongue is short-lived and relapse is apt to occur unless definitive therapy is started. While it is possible that nicotinic acid is a contaminant of the cozymase preparation, or that cozymase is broken down rapidly, liberating free nicotinic acid amide for some other function, the more plausible supposition is that the effect is produced so rapidly because cozymase is the actual form in which nicotinic acid achieves its unique function in the human body. Many more observations are needed to elevate this conjecture to the rank of fact.

The third patient got a rapid response after cozymase was given and then relapsed gradually over a nine-day period. We had an opportunity to observe rapid improvement in the tongue early in a course of ACTH therapy. It may be that the dramatic improvement was a coincidence, since we did not have complete dietary control. If the effect was indeed a specific result of ACTH, we can only speculate on possible mechanisms, and although adrenal function may be disturbed in pellagra,[7] presumably it stimulated the production of cortisone. Anabolic or anti-inflammatory responses might then explain it, or mobilization of enzyme systems, or improvement in assimilation; but it is idle to marshall all the possible speculations before so tenuous a filament of data.

Tryptophane, since it has occupied the position of stepchild in the vitamin family, is introduced to illustrate what turned out to be an unlikely solution of one of the many paradoxes of clinical nutrition. Our patient responded rapidly and well to relatively small doses of tryptophane, presumably because his margin of depletion was small.[8]

The notion that the tongue is a sensitive clinical indicator in pellagrous glossitis gains support from these observations. There is emphatic need for careful control or the observed changes may be misinterpreted. While the lingual change is a sensitive indicator, it does not have the specificity formerly ascribed to it, since several chemical compounds and the state of enforced rest may be responsible for

improvement in the pellagrous tongue in the direction of normal. Against this background we should view the alterations in the tongue in pernicious anemia and iron deficiency anemia with the specific correcting factors of liver, B_{12}, or folic acid for the one, and iron for the other. Details of the lesions and the response have been reviewed admirably by Darby[9] and Vilter,[10] where the emphasis has been, properly, on the usual therapeutic agents, rather than on the exotic group considered here. A tentative table of rough approximation gives the time of response with various agents in the pellagrous glossitis (Table I).

TABLE I
Time Required for Various Agents to Effect Improvement in Acute Pellagrous Glossitis

Cozymase	Few minutes to several hours
Nicotinic acid	Few hours to days
Tryptophane	Hours to days
ACTH + diet (uncertain)	1–3 days
Rest in bed	1–3 days
Crude liver extract	3–5 days
Yeast	3–15 days
Diet	3–20 days

We must emphasize that the observations recorded in this clinical progress report are not set forth as suggestions for practical therapy, but as examples of clinical research in the very difficult and perplexing field of human nutrition and malnutrition. The period of dietary control, with its treacherous change in sign and symptom for no apparent reason, and the danger of sharp aggravation of the disorder with its risk to the patient, is emphasized as a necessary precaution in investigation; it is a time when deterioration may upset the balance with disastrous speed unless the physician is constantly on the alert. The sheet anchor in therapy remains the good and ample diet, with vitamin supplements necessary but only in occasional instances lifesaving for their rapid effects.

Conclusions

We made clinical observations of the response of the tongue in pellagrous glossitis under conditions of dietary control, using cozymase, tryptophane, and ACTH as therapeutic agents.

Striking improvement was observed, but we have too few observations to permit general conclusions.

We emphasize the importance of a control period of observation before testing agents for therapeutic effect to avoid the nonspecific false positive response which may occur early during this period.

We do not recommend cozymase, tryptophane, or ACTH in the treatment of pellagra. Primary reliance rests on a good diet, supplemented with vitamins and the correction of underlying disorders of body or mind.

Appendix

Patient 1 was a 64-year-old woman who had had numerous admissions to the hospital, the first 8 years before her current admission for x-ray therapy for an adenocarcinoma of the cervix. She developed evidence of injury to the bowel, and 6 years later had a partial colectomy with anastomosis of ileum to transverse colon. Diarrhea, which began as intermittent episodes, became established with 10 to 12 watery stools a day. Though her appetite remained good and her diet theoretically adequate, her weight fell to 83 lbs. Weakness and easy fatigue plagued her. Red areas appeared on the back of the hands and arms, and would come or go without obvious cause. For several months she was troubled by burning and noticeable redness of the tongue. Toward evening her ankles swelled if she was on her feet much.

On examination we found a woman looking older than her chronological age, severely emaciated, lethargic but cooperative, and well oriented. She was too weak to walk. The skin of the legs was scaling with areas of "crazy-pavement" epithelium. Frequent use of a hot-water bottle had left her abdomen marked with the dark reticulated pigment of *erythema ab igne*. The backs of the hands were rough and darkly pigmented. The teeth were missing and her mouth had been too painful to wear her dentures. The tongue was bright red, swollen, and painful, and angular stomatitis and fissures marked the corner of her mouth. There was scarring and partial obstruction 3 centimeters within the rectum, and a scarred and

atrophic vagina almost closed by stenosis. No neuropathy was evident. The hemoglobin was 7 Gm.; red count 2,180,000 and white count 2150 per cu. mm.

She was kept in bed at rest for a three-day control period during which her tongue slowly lost its red color and edema, as may be seen in Figures 1A and 1B. Since her condition was precarious, we then gave her an excellent diet, supplemented with an ample supply of B complex vitamins, and the improvement continued.

PATIENT 2, a 35-year-old white woman, was studied on the medical wards. Six years before the current admission an operation for abdominal adhesions was done elsewhere. Two years later multiple fistulas formed with breakdown of the wound site. On August 12, 1947, she was admitted to the Surgical Service of the University Hospitals and hemicolectomy with resection of the distal ileum and ileocolostomy were performed. The tissues revealed an infectious granuloma. Postoperatively, a fecal fistula appeared. With special attention to diet, after discharge, her weight increased to 130 lbs. in spite of 5 to 8 stools daily. A year before the current admission she began to lose weight, diarrhea increased, and the tongue and mouth became sore. She weighed 90 lbs. on entry.

Examination disclosed an emaciated woman, looking much older than thirty-five. Her tongue was red, shiny and tender, and there was stomatitis. Blood pressure was 80/60. The skin was dry and cool, but there was no erythema or dermatitis. There was a draining fistula between the rectum and vulva. The hemoglobin was 6.5 Gm. and there was 1+ albumin in the urine. Serum albumin was 2.48 and globulin 2.01 mg. per 100 ml.

After a control period of three days, during which she ate little and vomited often, 25 mg. of cozymase were injected intravenously at a slow rate. Figures 2A and 2B show the change in the tongue after 24 hours. In addition to the return to a nearly normal color, the tongue and mouth lost their edema and the tongue its soreness. The subjective change was described voluntarily an hour after the injection. Changes in the color of the tongue were noticeable within three hours and were well established in 12 hours. Her skin felt warmer to the touch. There was a slow relapse during the next five days, but owing to her general condition we began active treatment including transfusion, vitamins, and high calorie, protein and vitamin diet. There was another change in the tongue, more gradual this time, but again reaching a nearly normal state after six days.

PATIENT 3 was a 79-year-old white woman with chronic arthritis whose diet for about a year prior to admission to the hospital consisted of coffee, fruit juice, and a rare slice of bread. She had lost much weight, developed a sore red tongue, and had some periods of diarrhea. Examination disclosed a pale emaciated woman with mixed arthritis, red, swollen, shiny tongue, poorly fitting dentures, several small aphthous ulcers of the buccal mucosa and pharynx and dry, inelastic skin without erythema or pigmentation. The liver was felt 7 centimeters below the rib margin. The urine was negative except for numerous white cells in the sediment. The hemoglobin was 10 Gm. per 100 ml., red cells 3,530,000 and white cells 7700 per cu. mm.

Although she was given a regular diet, she ate little and vomited every time she tried to eat. On the third hospital day 100 mg. of cozymase were given intravenously in 200 cc. of normal saline, and within 18 hours there was a decided change in the tongue. The purple red color disappeared, and the edema vanished, but the atrophy remained (Figs. 3A and 3B). She felt much better generally; her skin lost its cold clammy feel; and the ulcers in the mouth healed rapidly, having become painless within six hours of giving cozymase. Two days later she was eating her food fairly well and multiple vitamin preparations were given orally and parenterally. By the ninth day following cozymase therapy, in spite of the vitamins and modest increase in appetite, her tongue was once more red, boggy but not as painful as on entry, and appeared just as in Figure 3A. We decided to use ACTH to see whether it would change the tongue and improve the knees and other sore joints. On the 21st hospital day we began a program of ACTH injections, 25 mg. every 6 hours.

Gradually over a three-day period, the tongue lost its purple red color and smooth glistening appearance (Fig. 3C). There was another increase in sense of well-being; the joints improved and she gradually became able to walk again.

PATIENT 4 has been reported in detail elsewhere.[8]

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RESUMEN

Algunos aspectos de la lengua en la glositis pelagrosa

Se hicieron observaciones de la respuesta de la lengua en la glositis pelagrosa, bajo condiciones de control dietético, empleándose como medios terapéuticos la cozimasa, el triptofano, y la hormona adrenocorticótropa.

Una mejoría notable fué observado, pero las observaciones fueron insuficientes para permitir la formulación de conclusiones generales.

Los autores insisten en la importancia de un período control de observación antes de probar los efectos terapéuticos de estas substancias—para evitar la falsa respuesta positiva no específica que puede ocurrir tempranamente durante este período.

Los autores no recomiendan la cozimasa, el triptofano, o la hormona adrenocorticótropa en el tratamiento de la pelagra. El recurso principal tiene que ser una buena dieta, con suplementos vitamínicos y corrección de los trastornos subyacentes corporales o mentales.

Forgotten but not gone: Scurvy

"Since shortly before the war we have seen a gradual but steady loss of emphasis by physicians on nutritional deficiency diseases as such—not only in this country but abroad—if one excepts those areas which suffered significant restrictions in food consumption....

"That too complacent an attitude in this respect is not altogether warranted is suggested by the recent report of Follis, Park, and Jackson of a rather surprising amount of scurvy in children under two as determined by postmortem histologic examinations made in the years 1926 to 1942. Whether such a situation exists in older children is not clear, but the findings should serve as a warning."

—J. B. Youmans. *Journal of the American Dietetic Association* 28: 1029, 1952.

IRON DEFICIENCY *in* INFANCY *and* CHILDHOOD

By NATHAN J. SMITH, M.D.* AND SALVADOR ROSELLO, M.D.†

IRON DEFICIENCY is the most common nutritional deficiency encountered in children. The important factors responsible for this situation are the constant demand for iron in the growing child, the very low iron content of the foods which make up the bulk of the infant's diet, and the high incidence of "feeding problems." This report will present data concerning 162 infants and children with moderate to severe iron-deficiency anemia seen at St. Christopher's Hospital for Children. The clinical findings in these patients will define the problem of iron deficiency as it is commonly encountered. A small number of the patients have been studied extensively in an attempt to demonstrate some of the fundamental metabolic alterations present in this disease.

The 162 children were all in-patients on the pediatric service, most of them being admitted for conditions other than anemia. All of the patients included in this report had hemoglobin levels far below the range of normal for their age, the highest value being 9.9 Gm. per 100 cc. of blood. In each instance the anemia was found to be of the hypochromic, microcytic variety, characteristic of iron deficiency.

INCIDENCE

The most common anemia in infancy and childhood is that due to iron deficiency. From our clinical material we are not able to determine the overall incidence of iron deficiency in children, but its frequency at various ages forms an interesting and definite pattern. Figure 1 shows the age distribution of our cases. Very few infants were found to have a deficiency of iron before 6 months of age. The peak incidence (66 per cent) was in infants ranging in age from 9 to 24 months. The low incidence of iron-deficiency anemia in the preschool and school-age child is clearly demonstrated. Only 21 of the 162 patients were 4 years of age or older.

A consideration of the etiologic factors re-

AGE INCIDENCE OF 162 PATIENTS WITH IRON DEFICIENCY ANEMIA

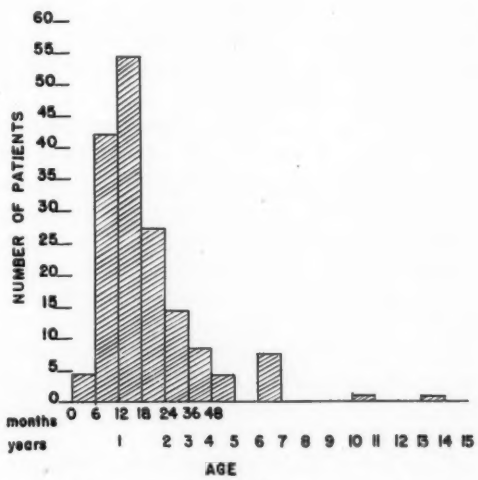

Fig. 1. The age incidence of 162 patients with iron-deficiency anemia. The disease is found with greatest frequency in infants 6 to 24 months of age. Iron deficiency would appear to be an uncommon cause of anemia in school-age children.

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sponsible for the development of iron-deficiency anemia provides an explanation of this striking age incidence pattern.

Etiology

In discussing the etiology of iron deficiency, one must consider conditions which disturb the normal iron balance of the body. It can be stated that a deficit in iron will result from either an inadequate supply of iron or an excessive demand for iron.

When iron deficiency is encountered in infancy it is usually the result of an inadequate supply of iron. Infants under 6 months of age are dependent upon iron deposited in their storage depots during intrauterine life. This supply of iron will not be adequate if the mother is markedly iron deficient, if her iron stores have been reduced by multiple pregnancies, if the infant is born prematurely, or if he is one of twins. Thus, the incidence of iron deficiency anemia is low in the first 6 months of life because of the relative infrequency of these causative factors.

After the age of 6 months the infant needs an exogenous source of iron to maintain an adequate hemoglobin level. At this time, the iron requirement is high because of rapid growth and because the iron stores have been depleted during the early months of life. This exogenous iron is supplied by foods containing significant quantities of iron.

The failure to add these foods to the diet by 6 months of age is extremely common for many reasons, which include feeding of excessive amounts of milk and cereals, poor feeding techniques, and behavior disturbances. Children with gastrointestinal disturbances may become deficient in iron even though they ingest an adequate amount of iron. Thus patients with chronic diarrhea, celiac disease, congenital anomalies of the gastrointestinal tract, ulcerative colitis, and the like are unable to absorb iron adequately.

Even though the supply of iron is adequate, an iron deficiency may develop if the demand is excessive. Because of the rapid growth of infants and children, the iron requirement is great, and it is difficult to say when this demand can be called abnormal. That this factor is important is evident from the fact that the greatest incidence of iron deficiency is found at the age when growth is most rapid, between 6 and 24 months. The demand for iron is also increased when iron is lost as a result of acute or chronic hemorrhage. Owing to the limited ability of the body to absorb iron even when the demand is increased, iron deficiency of varying severity will result. Iron deficiency resulting from blood loss may occur at any age of infancy or childhood, but hemorrhage is not as common an etiologic factor in children as it is in adults.

In our series of patients the importance of inadequate dietary intake of iron as a cause of iron deficiency in infants and children was clearly demonstrated.

In Figure 2 it will be seen that 147 of the 162 cases were found to have an inadequate intake of dietary iron. The diets consisted chiefly of milk and carbohydrates such as crackers, bread, cookies, and cereals. In 9 of these patients the effects of the improper diet were accentuated by inadequate fetal stores of iron.

In 10 infants under 23 months of age the iron deficiency resulted from inadequate storage of iron *in utero*. The patients had been born prematurely, were one of twins, or were born of mothers with severe iron deficiency. Three children had primary gastrointestinal disease which interfered with the absorption of iron to a sufficient degree to produce an iron-deficiency anemia. In 2 children recurrent blood loss produced an iron deficit.

Recently we have observed a small number of patients with iron-deficiency anemia in whom, after careful study, we are unable to inculpate any of the known causative factors as being responsible for the iron deficiency. Other workers have had similar experiences. Studies are in progress to try to explain these unusual situations.

Clinical Findings

The clinical findings associated with iron deficiency are difficult to define. In many hospitalized patients, the iron deficiency is a finding incidental or secondary to some other more disturbing complaint. The insidious on-

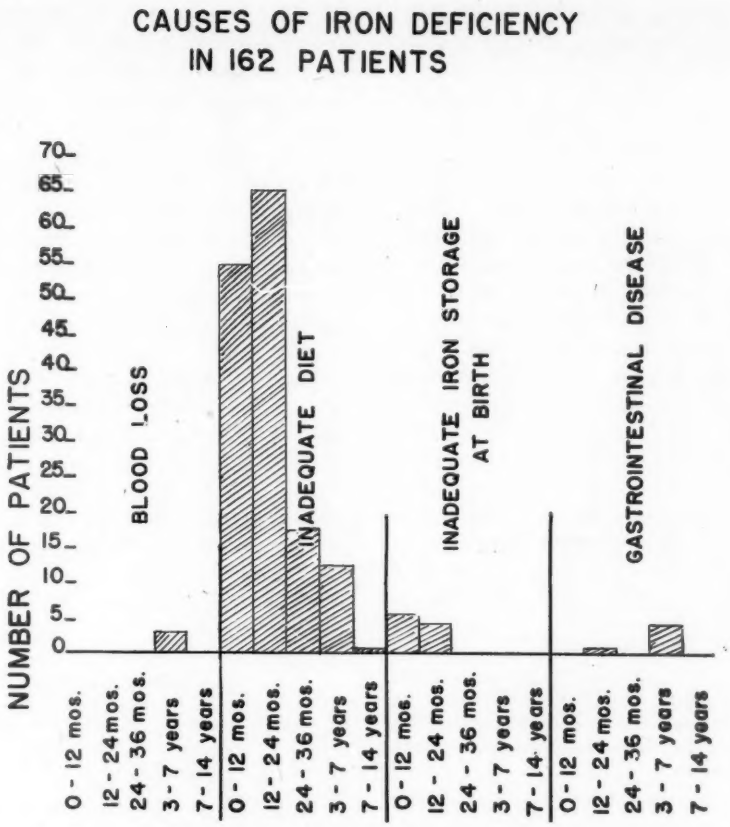

Fig. 2. An analysis of the etiological factors encountered in a series of patients with iron-deficiency anemia. Inadequate dietary iron intake is the most common cause of iron-deficiency anemia. Occasional instances of iron deficiency resulting from blood loss, gastrointestinal disease, and inadequate iron storage at birth were seen.

set of the deficiency and the remarkable ability of the body to adjust to very low hemoglobin levels may minimize the symptoms resulting from the iron deficiency *per se*.

In reviewing the histories of our patients, four symptoms were attributed to the iron deficiency and its resulting anemia. These were *pallor, irritability, anorexia,* and a *decrease in normal activity.* Figure 3 shows the frequency with which these complaints were encountered. In several patients there were no complaints which could be related to a deficit of iron, although their hemoglobin level was very low.

Anorexia, which we feel is due to the iron deficiency, is a particularly disturbing complaint. In iron-deficient infants the anorexia often leads to the establishment of a vicious cycle. The anorexia is responsible for the ingestion of an increasingly inadequate diet, which in turn leads to a more severe iron deficiency with more pronounced anorexia. That the anorexia is not due to the anemia *per se* seems likely, because this symptom is not present in children with anemia due to other causes. If iron is given in large doses intravenously, the anorexia is promptly relieved before any increase in the hemoglobin level occurs.

It is somewhat surprising that the severe anemia associated with marked iron deficiency does not inhibit the physical activity

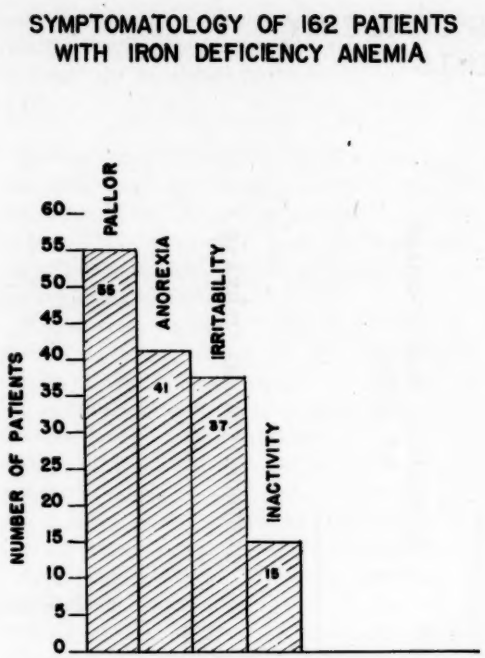

Fig. 3. The symptoms noted in 162 patients with iron-deficiency anemia were confined to pallor, anorexia, irritability, and loss of normal activity. The frequency with which these symptoms were encountered is shown above.

of some patients. Less than 10 per cent of our patients had a decrease in normal activity. By contrast, a large number of the children had become increasingly irritable as their iron deficiency and anemia had progressed. This was often a striking clinical finding.

A history of pica is not uncommon in these patients. Parents often bring the children to the clinic because of the child's ingestion of soil, foreign objects, stones, wood, etc. This symptom is relieved by correction of the iron deficiency. In studying such patients, one must consider anemia due to ingestion of some toxic substance such as lead, naphthalene, and other poisons. The true etiology of the anemia should become evident after appropriate blood studies have been completed.

The physical examination of patients with iron deficiency is often remarkable for the paucity of abnormal physical findings. The heights and weights of most of the children are adequate for their age, and many are actually overweight. Pallor was noted as a definite sign in 110 of our 162 patients, and was the most frequent abnormal physical finding. It is of interest that splenomegaly was found in 15 of the patients. The spleen was usually moderately enlarged, not exceptionally hard, and the edge was rounded. These patients all had some type of mild infection, commonly in the respiratory tract. Heart murmurs were frequently encountered. They were soft, systolic murmurs localized to the apex. Examination did not reveal any cardiac enlargement.

The epithelial changes so commonly seen in adults with iron deficiency were strikingly absent in the infants and children. Glossitis, koilonychia, loss of cutaneous elasticity, and changes in the texture of the hair were not found, nor were there symptoms of sideropenic dysphagia and esophageal changes described by Waldenstrom[1] as commonly occurring in adult patients. Esophagograms were not obtained.

Laboratory Studies

Since over 80 per cent of the iron in the body is involved in hemoglobin production, it is not surprising that the most striking finding in iron deficiency is inadequate production of hemoglobin. A decreased hemoglobin content of the individual erythrocyte is the specific pathologic change present in iron deficiency. The total number of circulating erythrocytes may be normal or only slightly less than normal but the hemoglobin level is always less than normal and may be markedly reduced. The anemia is, therefore, of the hypochromic variety. The hematocrit levels are lower than normal, and the cells as seen in a prepared blood film are small. A definite microcytosis is present. Therefore, the anemia of iron deficiency is a hypochromic, microcytic anemia. The familiar small, pale red blood cells of iron-deficiency anemia can be readily recognized in a stained smear of the peripheral blood as illustrated in Figure 4. A diagnosis of iron-deficiency anemia should not be made in the absence of this characteristic hypochromia and microcytosis.

In our patients the hemoglobin values

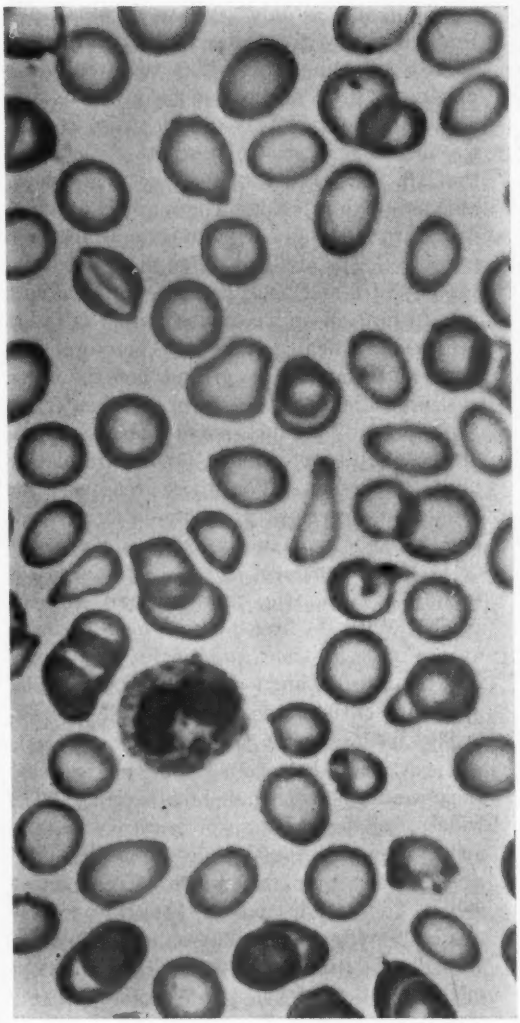

Fig. 4. A peripheral blood smear from a patient with moderately severe iron-deficiency anemia. The small, pale erythrocytes characteristic of iron-deficiency anemia are present. The platelets and leukocytes are normal.

ranged from 2.6 Gm. to 9.9 Gm. per 100 cc. Sixty-five of the 162 patients had hemoglobin levels of less than 50 per cent of the expected normal for their age. The lowest erythrocyte count was 1.27 million/cu. mm. However, only 2 of the 162 patients had erythrocyte levels below 50 per cent of the normal. A slight reduction in the erythrocyte count was usually found, but in every instance the anemia was hypochromic, with a color index of less than one. Reticulocyte counts were performed in 68 patients, and normal values were found in all instances.

The leucocytes showed no specific changes. The total leucocyte count was often elevated in response to some concurrent infectious process. Lymphocytosis, which has been reported in association with iron deficiency, was not demonstrated in our patients. Platelet counts were within the normal range.

The serum iron level was measured in 50 patients after a period of fasting of at least 12 hours. Figure 5 shows the results of these studies. The values ranged from a low level of 9.7 μg. per 100 cc. to a high value of 61.4 μg. per 100 cc. As can been seen from Figure 5, these values were lower than those of normal children. In the series of patients with iron deficiency reported by Vahlquist,[2] 15 of 20 patients had serum iron levels lower than normal when other evidences of iron deficiency were present.

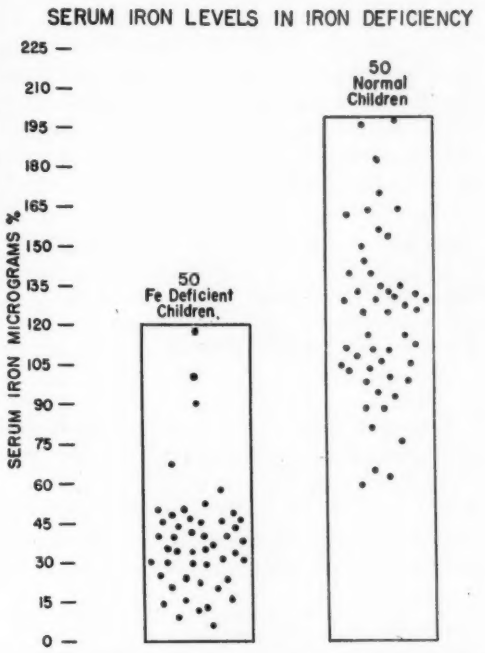

Fig. 5. The serum iron levels of 50 infants and children with iron-deficiency anemia are found to be lower than those found in 50 normal children.

Treatment

The treatment of iron-deficiency anemia is dependent upon the etiologic factor involved. If there is evidence of blood loss, the source of the bleeding must be corrected. If there is some primary disease in the gastrointestinal tract which interferes with the absorption of iron, the diagnostic and therapeutic procedures designed to eliminate the difficulty should be instituted. If the diet has been inadequate, specific steps must be taken to correct it. It is important to remember that supplementing the iron intake of a patient with medicinal iron is completely futile unless the cause of the iron deficiency is determined and corrected.

The correction of the iron-deficient diet in an infant or young child can be as difficult as it is important. The problem is to satisfy a major part of the caloric requirement with iron-containing foods. Primarily, this means the exclusion from the diet of foodstuffs low in iron content, e.g., milk, cereals, and carbohydrates. Potatoes, spaghetti, bread, cookies, crackers, and cereals should not be given, although these foods are favorites of young children. They contain very little iron. Because such foods are high in caloric value, they readily satisfy the patient's appetite. The following corrective diet is prescribed for older infants and young children.

Breakfast	*Lunch*	*Supper*	*Bedtime*
4 oz. milk	4 oz. milk	4 oz. milk	4 oz. milk
Egg, crisp bacon	Meat soup	Meat	Fruit
Fruit	Raw vegetable	Vegetable	
	Fruit	Stewed fruits	

The milk intake is limited to one pint daily, and after an adjustment period of a few days the patient satisfies his appetite with this more adequate diet. After this adjustment has been made, the patient is given some supplemental form of medicinal iron.

Use of Iron

In the human, ferrous iron is absorbed more efficiently than iron in the ferric form.[3] Thus, in prescribing an iron supplement, a ferrous salt is used. As only a relatively small percentage of any given dose of iron can be absorbed, it is important that the total daily amount of iron medication be given in 3 or 4 divided doses. This practice also reduces the incidence of gastrointestinal disturbances that are associated with the ingestion of large amounts of iron salts. The manner in which the material is given is of the utmost importance. The ability of phosphorus-containing phytates and phosphates to combine with iron to form insoluble, unabsorbable salts has been clearly demonstrated.[4] Therefore, it is important that iron be given when the upper gastrointestinal tract is free of these materials. Milk and milk products contain large amounts of phosphates; cereals and breads are high in phytate content. For these reasons, iron should be prescribed as a simple ferrous salt and should be given in 3 or 4 divided doses each day. The supplement should be taken in the fasting state in the morning and between meals. With the iron preparations available at the present time, practically no gastrointestinal disturbances due to the iron supplement are encountered.

The treatment of iron-deficiency anemia with compound hematinic, "shotgun" preparations cannot be condemned too severely. The widespread use of these preparations reflects no honor on the medical profession. The "dilution" of such preparations with liver extract, cobalt, folic acid, and most of the readily available vitamins, makes it impossible for a pediatric patient to ingest a sufficient quantity of many of these preparations to give an adequate therapeutic dose of iron. If such material is given to an anemic patient before a specific diagnosis is made, the suboptimal effect on the hematopoietic system will result only in future studies being inconclusive or misleading. Furthermore, when nonspecific, compound preparations are used the cost of treatment may be increased more than ten times. *When iron is indicated give only iron.* The therapeutic response will be infinitely better, the medication will be taken with greater facility, and the cost of treatment will be far less.

Recently an iron preparation suitable for

intravenous administration has become available. There are few indications for the use of such parenteral iron in infants and children. Toxic manifestations such as fever, nausea and vomiting, hypotension, and convulsions may accompany its administration. The multiple venipunctures involved in a full course of treatment are disturbing to both patient and doctor. This material is indicated in patients with uncorrectible gastrointestinal disturbances where oral iron is not effective or in other situations where oral iron medication cannot be given.

Discussion

In this presentation, no attempt is made to review the extensive work which has been carried on concerning the problems of normal iron metabolism. The early work with animals has been supplemented by many studies in human adults. However, at the present time, relatively few data are available concerning the many aspects of iron metabolism peculiar to children.

The inability of the body to excrete iron in any significant amount is a prime consideration in our understanding of iron metabolism. Extensive studies both in animals and in man have shown that only a negligible amount of iron is excreted in the urine, stool, or in perspiration.[4] The adult male will lose slightly more than one milligram of iron daily, the larger part of this being lost by the normal exfoliation of epithelial cells. Because of menstrual blood loss, the average daily iron loss in the female is approximately two milligrams. Because of the absence of any mechanism by which the body can normally lose iron, it has been concluded that the development of an iron deficiency in an adult subject must result from actual blood loss.

Most of the electrolytes in the body are absorbed in relatively large quantities from the intestinal tract, and amounts in excess of the body needs are excreted. Such conditions do not apply in the metabolism of iron, and the iron content of the body must be regulated by rigid control of the amount of iron that is absorbed into the body. That such a control mechanism does exist has been proposed by Granick and his colleagues,[5] who postulate the existence of a "mucosal block" operating in the mucosal cells of the upper gastrointestinal tract where iron is normally absorbed. It is proposed that the ability of the mucosal cells to absorb iron is controlled by their ability to form a stable iron-protein complex called ferritin. When the duodenal mucosal cells are saturated with ferritin, no more iron is absorbed. These findings are in keeping with the generally accepted fact that iron is absorbed in proportion to the body's demand for iron. In the iron-deficient subject relatively large amounts of iron are absorbed, whereas in patients with hemosiderosis following many blood transfusions very little iron is absorbed. Recent studies by Dubach, *et al.*[6] have challenged the complete effectiveness of the "mucosal block" and question the importance of this mechanism in regulating the iron content of the body.

It appears that the ability of the body to absorb iron is quite limited, even in the face of increased demands for iron. From the large amount of iron ingested in the normal diet each day (5–10 mg.), the adult will absorb between 1 to 2 milligrams. In iron deficiency, where the demand for iron is great, the absorption of iron administered in commonly-used therapeutic doses has been found to be only 5 to 10 per cent of the total dose.[7] Iron is thought to be absorbed in the ferrous state, and conditions in the upper gastrointestinal tract which enhance the conversion of the ferric iron of food to the ferrous state increase its absorption. Normal gastric acidity would appear to be important in this regard, as well as the presence of reducing substances ingested in the diet. Moore recently demonstrated increased absorption of iron from diets containing added amounts of ascorbic acid.[8]

Beyond the first portion of the duodenum the pH of the intestinal contents rises, and insoluble, unabsorbable hydroxides of iron are formed. Thus, except in most unusual circumstances, iron is absorbed almost entirely in the first portion of the duodenum. Many workers have investigated the effect of

various food substances on the absorption of iron. The ability of phosphorus compounds such as phosphates and phytates to inhibit the absorption of iron has been clearly demonstrated.[9] The ability of ascorbic acid to increase iron absorption has been mentioned. Finch *et al.* fed extremely deficient diets of corn grits and lard to dogs and found that iron added to such diets was absorbed in increased amounts.[10] Ligation of the pancreatic duct in animals has also led to the increased absorption of iron—presumably because of the resultant changes in the pH in the duodenum.

After iron is absorbed into the mucosal cells of the duodenum it must be transported to the sites of storage or utilization. Iron in a "free" state, i.e., unbound to protein, is not tolerated by the body. Thus, during transport, iron is bound to a specific metal-binding plasma globulin (Siderophilin, Cohn Fraction IV-7). In the normal individual there is enough of this material present in the serum to combine 2.5 to 4.0 μg. of iron per cc. of plasma. Under normal basal conditions approximately 30 per cent of this protein is saturated with plasma iron in transport. This remarkable protein appears to have the ability of receiving and transporting and finally of releasing iron at the sites of storage and utilization. It is important to realize that the amount of iron-binding protein in the plasma appears to be the limiting factor in determining how much iron the plasma can transport at any given moment.

In the normal adult, a variable amount of iron is assimilated in excess of that needed for immediate hemoglobin production and for other body functions. This iron is held chiefly in the parenchymal and reticulo-endothelial cells of the liver and spleen as storage iron. The iron in the cells is combined with a specific protein called apoferritin and the resultant compound is called ferritin. If amounts of iron accumulate in these tissues in excess of the amounts of available apoferritin, large amounts of iron are attached to the ferritin molecule and a large iron-containing molecule called hemosiderin is formed. The large iron-containing masses of hemosiderin are readily seen histologically, whereas ferritin is not visible. Both forms of storage iron are available for hemoglobin production when a need for increased amounts of iron arises.

Of the 3.0 to 5.0 Gm. of iron present in the adult male, approximately 60 per cent is present as hemoglobin iron and 20 per cent is present as storage iron available for hemoglobin formation. Thus, nearly 80 per cent of the body iron is concerned with hemoglobin production.[11] Approximately 25.0 mg. of iron are needed daily for the production of new hemoglobin in the adult. As only one or two milligrams of iron are absorbed daily, it is evident that iron is used over and over again for hemoglobin production. The iron needed for hemoglobin synthesis is obtained almost entirely from the iron liberated in the destruction of worn-out erythrocytes. Of the small amount of iron that is absorbed and enters the plasma in the normal individual, 75 to 90 per cent will be utilized promptly for hemoglobin production.[12] The iron deposited in the storage depots is called upon for formation of hemoglobin only when the iron from these other two sources is inadequate.

Iron Metabolism in Children

These thoughts on the normal metabolism of iron have been derived from extensive animal experimentation and studies on adult subjects. How the immaturity and rapid growth which characterize the pediatric subject influence these phenomena is not known. Certainly the constantly and rapidly increasing size of the erythrocyte mass must result in a relatively great demand for iron. Unless future studies show that infants and children have a more efficient mechanism for the absorption of iron, the margin between adequate and inadequate amounts of iron available for normal body functions must be small indeed. It may be that normal children are relatively iron "deficient" when compared to adult subjects. The frequency with which infants and young children become iron deficient when their dietary intake of iron is inadequate emphasizes the need for a relatively large intake of iron during the growth phase.

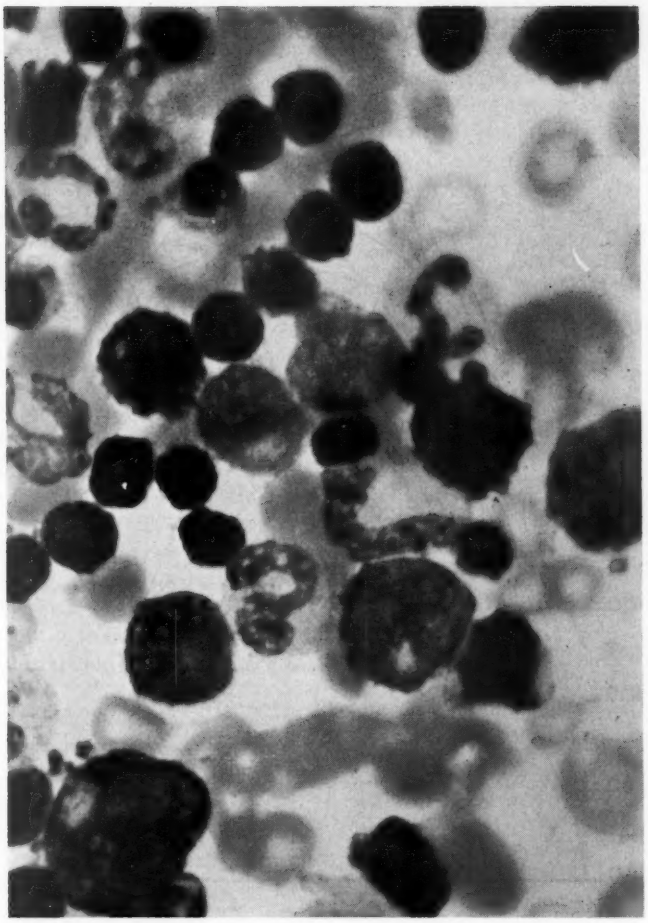

Fig. 6. A smear preparation of aspirated bone marrow. Many normoblasts are seen with only small amounts of very poorly hemoglobinized cytoplasm.

The period of birth to 2 years of age is a particularly interesting one in regard to iron metabolism. During this age, growth is extremely rapid and the iron content of the diet very low. For the first 3 to 6 months of life the infant exists on a diet of milk and cereals. Neither of these materials contains significant amounts of available iron. During this period of time the body weight and the total hemoglobin mass are doubled. The large amount of iron needed in this situation is derived from storage iron accumulated during intrauterine life. Mechanisms involved here have been studied recently by Smith[13] and by Vosburgh and Flexner.[14] These workers have shown that maternal plasma iron rapidly crosses the placental barrier and the iron, thus acquired, is used for hemoglobin production for at least 4 months after birth. If any situation arises which will interfere with the normal storage of iron *in utero*, the infant is apt to become iron deficient in the first year of life. Premature infants and those resulting from multiple births, or infants born of mothers who are iron deficient, will frequently develop severe anemia owing to inadequate storage of iron *in utero*.

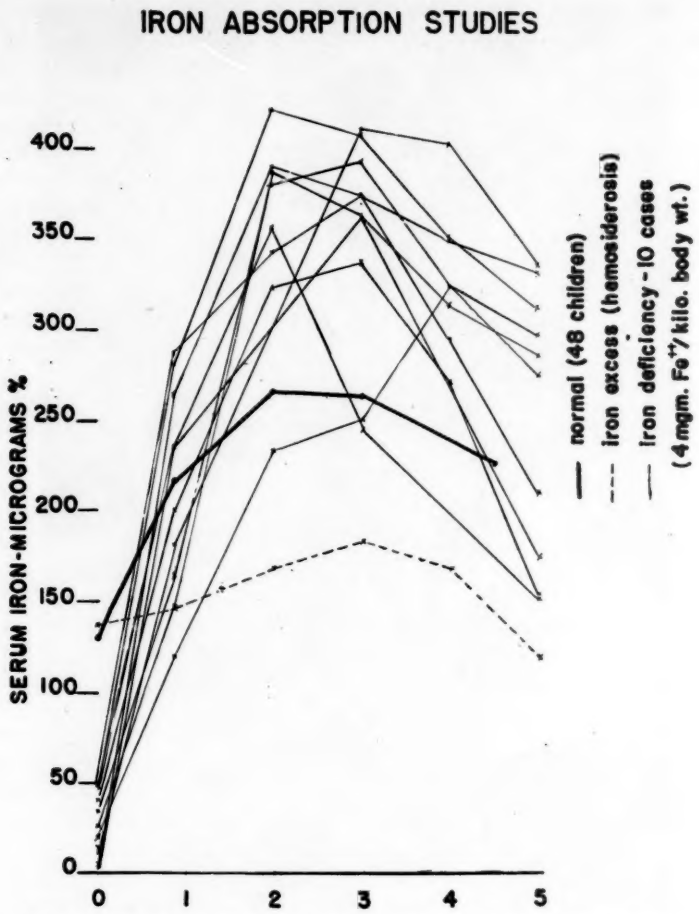

Fig. 7. The absorption of iron after oral ingestion of ferrous iron (4.0 mg./Kg body weight). The serum iron level is measured at hourly intervals (see text).

A series of clinical and laboratory observations in certain patients with iron-deficiency anemia have allowed us to demonstrate a number of physiological alterations present in young subjects with this disease. We have examined specimens of aspirated bone marrow in several of the patients with iron-deficiency anemia. Defective hemoglobin production in the developing erythrocytes may be readily demonstrated morphologically. The bone marrow attempts to compensate for the anemia by proliferation of erythroid elements. The typical picture is one of late normoblastic proliferation, with the normoblasts having sparse, irregular amounts of cytoplasm deficient in hemoglobin. These changes are illustrated in Figure 6.

One of the most striking compensatory changes present in the iron-deficient child is the ability to absorb increased amounts of iron from the gastrointestinal tract. By having patients ingest a standardized amount of a ferrous salt and measuring the changes in the serum iron level at repeated intervals, a relative measure of iron absorption may be obtained. Such experiments have been performed in patients with iron-deficiency anemia as shown in Figure 7. The rapid marked

elevation of the serum iron level, when compared to the data on absorption in nonanemic children, indicates an increased absorption of iron in the iron-deficient patients. Two patients, who have an excessive amount of iron in their tissues as a result of having received repeated transfusions in the treatment of Mediterranean anemia, absorb very little iron.

The peaks of the absorption curves in patients with iron-deficiency anemia are not much higher than the highest values found in control subjects. This is the result of the ability of the plasma to carry only as much iron as can be bound to the specific iron-binding protein. Wintrobe, Cartright *et al.* have demonstrated an increase in the iron-binding protein in plasma of iron-deficient subjects. In their subjects a 50 to 100 μg. per cent increase was noted in the plasma-binding capacity. This is in keeping with our findings. Because of inability to obtain reproducible results with current methods of determining the serum iron-binding capacity we have not supplemented our observations with such studies.

At the present time, information is lacking regarding abnormalities in iron-containing substances, other than hemoglobin, in iron-deficient children. Fifteen to 20 per cent of the total body iron is present in muscles as myoglobin and as part of many vital enzyme systems (catalase, peroxidases, etc.) in parenchymal cells throughout the body. No satisfactory method is available to measure specifically the effect of iron deficiency on the function of such substances. Clinical observations of patients with severe iron deficiency would lead us to suspect that there are unidentified abnormalities in the general body metabolism in iron-deficient subjects other than those related to the anemia. Occasionally we have given iron intravenously to children with severe iron-deficiency anemias who had marked anorexia, striking irritability, and who were completely unable to maintain normal activity. These symptoms of iron deficiency were corrected in 24 to 36 hours by the administration of iron intravenously. Before the hemoglobin level changed, the patients began to eat, were no longer irritable, and became much more active. Such observations suggest very strongly that there are widespread changes in the body in iron deficiency states other than those caused by the anemia, *per se*.

Summary

The clinical aspects of iron-deficiency anemia in infants and children have been discussed. One hundred and sixty-two cases of iron-deficiency anemia have been used to illustrate certain features of the disease.

Children are prone to develop iron deficiency because of (a) their rapid growth and consequent great demand for iron, (b) the low iron content of normal diets in early life, and (c) the common occurrence of "feeding problems" in late infancy and early childhood.

The laboratory findings in iron-deficiency anemia are presented and treatment is discussed.

The present knowledge of iron metabolism is reviewed and a brief discussion of the changes in iron absorption and utilization in iron-deficient children is presented.

That there are abnormalities in iron-deficiency states other than those which can be attributed to the anemia *per se* is suggested by clinical observations of the effect of large doses of parenterally administered iron to children with severe deficiency of iron.

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Resumen

Sideropenia en la infancia y en la niñez

Se consideran los aspectos clínicos de la anemia sideropénica en infantes y niños. 162 casos de anemia sideropénica sirven para ilustrar ciertos caracteres de esta enfermedad.

Deficiencias de hierro tienden a manifestarse en los niños por (a) su crecimiento rápido y consiguiente alto requerimiento de hierro, (b) el bajo contenido en hierro de las dietas normales en los primeros años de la vida, y (c) la ocurrencia frecuente de "problemas alimenticios" en la infancia y en los primeros años de la niñez.

Se presentan los hallazgos de laboratorio en la anemia sideropénica, y el tratamiento apropiado se considera.

Se pasa revista al conocimiento actual del metabolismo del hierro, y se presenta una breve descripción de los cambios de absorción y utilización del hierro en los niños sideropénicos.

Que hay abnormalidades en los estados sideropénicos además de las que se pueden ascribir a la sola anemia lo sugieren observaciones clínicas del efecto de la administración parentérica de grandes dosis de hierro a niños con sideropenia severa.

TIME FACTORS in the Utilization of a Mixture of AMINO ACIDS (PROTEIN HYDROLYSATE) *and* DEXTROSE *Given Intravenously*

By ROBERT ELMAN, M.D.

THE STUDIES of Schoenheimer[1] several years ago added impetus to a dynamic rather than a static concept of the metabolic changes in the body, including the behavior of exogenous nutriments. As one views the nutritional process as a constantly changing metabolic pool, it is natural that certain time factors might be found to play an important part in the utilization of food elements. Of these, one might be thought of as dealing with the relative time at which each element entered the pool (in respect to other elements), another with the rate of time it took for each to be absorbed. In the present report, evidence obtained in the human will be presented to show that both factors influence nitrogen balance following the intravenous infusion of amino acid mixtures.

PREVIOUS WORK

It has long been known that the most efficient utilization of protein food requires sufficient carbohydrate and fat. It was only in 1937 that Larson and Chaikoff[2] first showed that there was a time factor in this relationship, i.e., that to achieve nitrogen balance with a given diet required the synchronous administration of its protein and nonprotein components. In animals, they observed a loss of nitrogen if the nonprotein portion was ingested 4 hours before or 4 hours after the ingestion of the protein portion. This phenomenon was confirmed in humans by Cuthbertson and Munro[3] two years later. Among other things, these workers found that the separate administration of carbohydrate and protein resulted in a loss of up to 2 Gm. of nitrogen a day, as compared with the achievement of positive balance when both were given together. More recently (1949) Leverton and Gram[4] made similar observations in 14 healthy human subjects subsisting on a well-balanced diet of three meals a day, but in which the breakfast contained little or no protein. By merely including protein in the breakfast meal, reducing by the same amount the protein content in the two other meals, nitrogen balance was improved by an average of 0.7 Gm. per day, a value which was statistically significant.

A similar time relationship has been observed in the utilization of amino acids themselves through experiments in which some were given separately rather than all simultaneously. This phenomenon was first demonstrated by the author[5] in 1939 during studies on the intravenous infusion of amino acid mixtures. A complete mixture which led to nitrogen balance failed to do so when its

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tryptophane component was injected 6 hours after the administration of the others. Confirmation came in the work of Cannon,[6] who observed that protein synthesis failed when two groups of essential amino acids were fed separately as compared with normal synthesis when all were fed together. Geiger,[7] in even more extensive studies, reported the same findings. For example, adult rats were fed for 12 hours on a tryptophane-free diet and the missing amino acid was then fed 12 hours later. These rats lost weight as fast or faster than control rats receiving no amino acids at all. Schaeffer and Geiger[8] found that cataract which develops in tryptophane-deficient rats could be prevented only if tryptophane was added to the protein moiety of the diet and not if added later. These observations are really not surprising in view of the older physiological studies of Van Slyke, Cullen and McLean,[9] who found that the first amino acids reaching the liver from the gastrointestinal tract are deaminized and their nitrogen excreted very rapidly without awaiting further absorption of other amino acids necessary for protein synthesis. This obviously wasteful process means that there is no mechanism by which certain amino acids can be stored in the liver or elsewhere until the arrival of others necessary for protein synthesis. That these considerations may have practical significance is suggested by the studies of Chase and Lewis,[10] who showed some time ago that in white rats some amino acids are absorbed much more slowly than others. For example, glycine was absorbed three times faster than the leucines. In a review in 1931, Cori[11] called attention to the influence of a poor general condition of the animal on intestinal absorption of various nutriments, so that when two were fed simultaneously, the rate of absorption of each was greatly reduced.

Even if all the amino acids were absorbed at the same rate and reached the liver and other tissues simultaneously, the inability of tissue to store amino acids can still influence protein synthesis whenever large amounts are absorbed or infused within a short period. This phenomenon was studied and evidence obtained by Geiger[12] to show that "When the rate (of supply) is too fast, utilization will suffer because no excess of amino acids can be stored normally for later use; the surplus is either excreted or irreversibly metabolized." Geiger's evidence emerged from studies with diets in which varying rates of intestinal digestion and absorption could be correlated with varying rates of growth of immature rats. All animals received the same basal diet except that the protein component was different, though each was of equal biological value. The best growth was obtained with the protein which required the longest period of time for digestion and absorption. For example, although skimmed milk protein had the same biological value as lactalbumin itself, the former gave a better growth curve. Study of gastrointestinal function showed that 91.5 per cent was still in the stomach 2 hours after feeding the former, as compared with only 60 per cent in the case of the latter.

Gastrointestinal motility is notably slowed by the ingestion of fat, and Geiger postulated that this may explain the influence of fat on the utilization of both carbohydrate and protein. For example, Nieft and Deuel[13] found the rate of galactose utilization varied directly with the percentage of dietary fat, which prolonged the period of absorption. The observations of Swanson[14] showing that fat decreases the loss of nitrogen on a subcaloric nonprotein diet may perhaps also be due to a similar mechanism in prolonging the period of intestinal absorption, and hence utilization of the ingested carbohydrate.

As to protein utilization, Geiger found that in immature rats receiving a given amino acid ration, added fat gave better growth than added glucose, each in isocaloric amounts. Schwimmer and McGavack[15] also found better nitrogen balance in humans on a 900 calorie diet containing 6 Gm. of protein nitrogen when 30 per cent of the food in the diet contained fat, as compared with a diet in which only 10 or 20 per cent contained fat by weight. It is true, of course, that the ingestion of fat may influence the metabolism of other nutrients in many ways. Nevertheless, its action in prolonging the period of gastrointestinal absorption must surely have an important bearing on

the time factor in the utilization of protein.

This time factor does not deal with the degree of digestion or absorption, which in any case may be all but complete; it deals merely with the time interval required for complete digestion and absorption, i.e., the rate at which amino acids enter the metabolic pool. One wonders whether many of the differences noted in the literature in growth and in nitrogen balance on various protein foods might not have been due in part to the rate with which the protein food was digested and absorbed, rather than to supposed differences in biological value or amino acid composition.

Present Observations

The present observations concern nitrogen balance data obtained during thirty-three 24-hour periods in 4 patients, one a well-nourished female studied before and after operation, the other three malnourished individuals in a relatively uniform clinical state. Two kinds of experiments were carried out as follows.

1. Amino acids and glucose given separately. In this experiment, three periods of 3 or 4 days each were compared in the same patient. During the first period, 2 liters of 10 per cent glucose (200 Gm.) were infused intravenously, 1 in the morning, 1 in the afternoon. During the second period, 2 liters of a mixture of 5 per cent glucose (100 Gm.), 5 per cent amino acids* (100 Gm.) were infused, 1 liter in the morning, 1 in the afternoon. During the third period, 1 liter of 10 per cent amino acids (100 Gm.) was given in the morning, 1 liter of 10 per cent glucose (100 Gm.) in the afternoon. The rate of infusion (5 ml./Kg./hr.) was the same in all cases.

2. Amino acids and glucose given together but at different rates. In this experiment, 3 patients were used, all receiving daily infusions of 2 liters of 5 per cent amino acids, 5 per cent glucose. In the first patient the 2 liters were infused during 8 hours and 4 hours on alternate days before and after operation. In the second and third patients, the infusion was given for 3 or more days at a slow rate (19 to 24 hours) followed by a period of 3 or 4 days at a faster rate (8 to 9 hours).

Urine output was carefully collected for each 24-hour period, its volume measured and an aliquot saved for determination of creatinine by a spectrophotometric modification of the Folin method and nitrogen by a macrokjeldahl procedure.[16]

Findings

Findings are shown in Figure 1 and in Tables I, II, and III.

In the first experiment (Fig. 1), the importance of infusing glucose and amino acids together rather than separately is strikingly illustrated, thus confirming previous observations by many others, as already discussed.

Of additional interest was the fact that when 100 Gm. each of amino acids and glucose were given together, no glycosuria resulted, whereas when the same amount was given separately, 14 to 18 Gm. of glucose appeared in the urine each 24 hours.

It should also be noted that the intake during this entire experiment was subcaloric. Despite this, positive nitrogen balance was observed during the 3 days in which amino acids and glucose were given together.

The second group of experiments were all consistent in showing a better nitrogen balance during periods when the mixture of amino acids and glucose was infused slowly, as compared with periods in which the infusion was more rapid. Findings in the first patient (Table I) show an average daily nitrogen balance of +1.8 Gm. during a 3-day period when the infusion occupied the entire 24 hours, as compared with an average daily nitrogen balance of −1.0 Gm. during a 3-day period when the infusion lasted but 9 hours out of the 24. Analysis of the individual figures for each day showed no overlapping, thus making the average difference of statistical significance. The findings in the second patient are shown in Table II, and here the differences are even more striking—a balance of +5.4 as compared with +0.7 during the periods of slow and rapid infusion, respectively. Here, too, there was no overlapping in the values for each day, thus making the averages of statistical significance.

* Amigen,® a protein hydrolysate, was used throughout the present study, except where stated otherwise.

The findings in the third patient are shown in Table III. Here there was a less pronounced time difference between the long and short infusions (8 as compared with 4 hours), which were carried out on alternate days, both before and after operation. Nevertheless, the difference in nitrogen balance was definite, an average of —4.3 as compared with +0.7 during the periods of short and long infusion respectively. Analysis of the individual daily values also shows no overlapping, which makes the averages of statistical significance.

It should be mentioned that in both of the first two experiments in this group (data in Tables I and II) the long infusion was given first. It would have been better had the order been reversed in one of them. Whether this factor would have made any difference can only be determined by further study.

It is of interest to note that despite an inadequate caloric intake, nitrogen balance was positive in all but three of the fifteen 24-hour specimens in the first 2 patients (Tables I and II). This was undoubtedly due to the fact that both of these patients were extremely malnourished. In the experiment on the third patient (Table III), who was well nourished, nitrogen balance was positive in only two of the six 24-hour specimens, and was negative even before operation. The influence of the

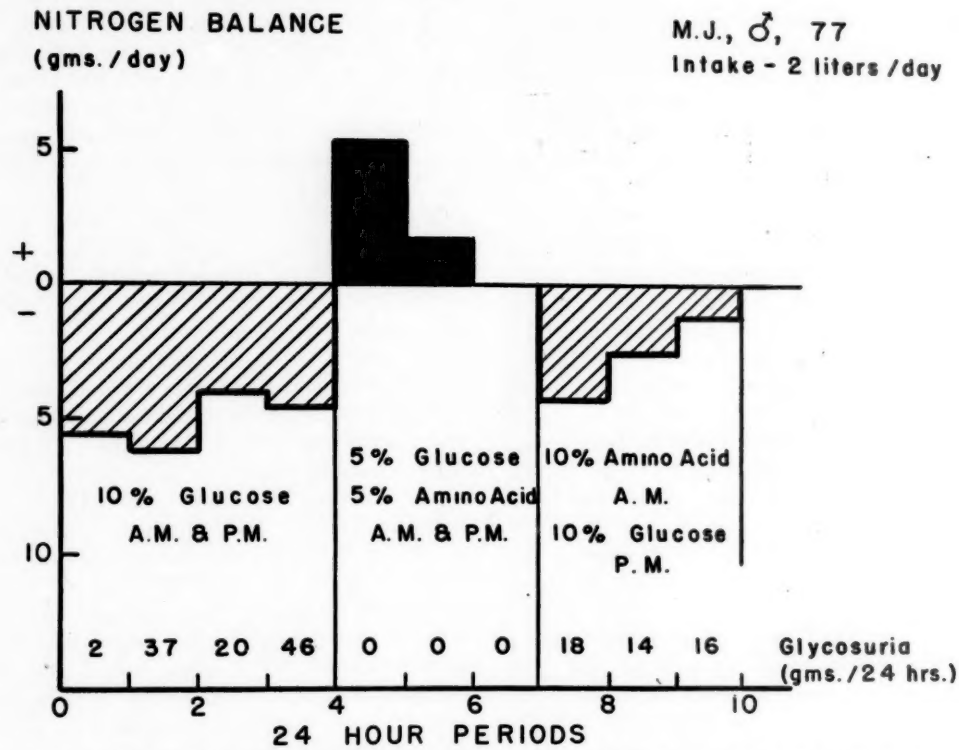

Fig. 1. Nitrogen balance when amino acids and glucose are infused separately. The patient whose findings are shown above suffered from inoperable carcinoma of the stomach and could take nothing by mouth. He was in a relatively stable clinical condition at the time of the above observations.

Note that positive nitrogen balance was achieved during the mid-period during which glucose and amino acids were mixed, whereas the same total amount of amino acids and glucose given separately during the third 3-day period resulted in negative nitrogen balance. Note also the data on glycosuria showing a large loss when 200 Gm. of glucose were given, a moderate loss when 100 Gm. each of glucose and amino acids were given separately, and no glycosuria at all when 100 Gm. each of amino acids and glucose were given together.

TABLE I

Nitrogen Balance with Amino Acids and Glucose Infused at a Slow and Fast Rate During Succeeding 3-Day Periods

G. F. 37 F Stricture of common duct

Consecutive 24-hour periods	Period of infusion	24-Hour output		24-Hour-urinary output		Total N output*	Remarks
		Urine	Gastric secretion	Creatinine	Glucose		
	Hrs.	*L.*	*L.*	*Gm.*	*Gm.*	*Gm.*	
1	24	0.72	0.60	0.49	11	8.3	Weight 39.5 Kg.
2	24	0.91	0.64	0.62	14	10.2	
3	24	1.1	0.72	0.58	14	12.1	
Daily average	24	0.91	0.63	0.56	13	10.2	Nitrogen balance +1.8
4	9	1.9	0.57	0.89	20	13.1	
5	9	1.2	0.64	0.66	33	13.7	
6	9	1.4	1.0	0.57	12	12.3	Weight 39.6 Kg
Daily average	9	1.5	0.70	0.70	22	13.0	Nitrogen balance −1.0

N.B. Daily intake—2 liters 5% glucose, 5% Amigen®,
1 liter Ringers solution,
N = 12.0 Gm.

* Includes nitrogen output in gastric secretions.

TABLE II

Nitrogen Balance with Amino Acids and Glucose Infused at a Slow and Fast Rate During Succeeding 6- and 4-Day Periods

J. F. 52 F Pancreatic fistula

Consecutive 24-hr. periods	Periods of infusion	24-Hr. urinary output				Remarks
		Volume	Creatinine	Glucose	Nitrogen	
	Hrs.	*L.*	*Gm.*	*Gm.*	*Gm.*	
1	17	1.0	0.14	5	3.7	Weight 31.8 Kg. Blood 500 ml.
2	16	2.3	0.43	12	8.8	Blood 500 ml.
3	23	1.4	0.28	7	5.2	
4	23	1.2	0.40	12	8.1	
5	20	—	—	—	—	(Specimen lost)
6	19	1.2	0.43	24	10.1	
Daily average	19	1.4	0.33	12	7.2	N bal. +5.4
7	11	1.7	0.53	17	11.1	
8	8	1.2	0.48	12	11.4	
9	9	1.0	0.41	11	10.0	
10	8	2.0	0.62	21	15.1	Weight 31.8 Kg.
Daily average	9	1.8	0.50	15	11.9	N bal. +.7

N.B. Daily excretion of pancreatic juice 90 to 300 ml. Nitrogen content (maximum 0.17 Gm.) added to urinary output of nitrogen.
Daily intake—2 liters of 5% Merck amino acids, 5% glucose I.V.,
(Nitrogen = 12.6 Gm.),
200 ml. ice water orally.

TABLE III

Pre- and Postoperative Nitrogen Balance with Amino Acids and Glucose Infused at Varying Rates on Alternate 24-Hour Periods

V. W. 29 F Cholecystectomy

Pre- & postoperative 24-hr. periods	Periods of infusion	24-Hr. urinary output				Remarks
		Volume	Creatinine	Glucose	Nitrogen	
	Hrs.	*L.*	*Gm.*	*Gm.*	*Gm.*	
—2	8.2	1.1	0.66	5	9.0	
—1	4	1.2	0.88	12	14.3	Weight 55 Kg.
1	7.7	0.7	0.75	12	13.1	
2	4.2	1.1	1.06	26	16.9	
3	8.7	0.8	0.64	6	11.9	
4	5	1.1	1.2	12	17.7	Weight 54.4 Kg.
Daily average with short infusion	4.4	1.1	1.05	17	16.3	N balance—4.3
Daily average with long infusion	8.2	0.9	0.68	8	11.3	N balance—+.7

Daily intake—2 liters 5% glucose, 5% Amigen®.
N = 12.0 Gm.

state of nutrition on protein utilization has been clearly demonstrated by Allison,[17] who found that positive nitrogen balance on an inadequate caloric intake is readily achieved in depleted, but not in well-nourished, animals.

Of additional interest in the findings listed in Tables I, II, and III was the excretion of creatinine. In all three cases, more creatinine was excreted during the shorter periods of infusion when the urinary nitrogen was also higher. It is generally stated that sudden falls in creatinine excretion indicate that portions of the urine have been lost. However, scrutiny of the present observations shows that this was not the case, as indicated by the uniform urine volumes collected. However, the use of creatinine excretion as an indication that the 24-hour urine collection was complete is presumably valid only when the nitrogen excretion is constant and the clinical condition stable. It has long been known that creatinine excretion is increased after trauma, along with the increased nitrogen excretion due to increased breakdown of protein tissue. The present observations, which we have made many times before, show that creatinine excretion may also increase whenever there is an increased excretion of nitrogen in the urine because of a greater breakdown of infused amino acids.

Comment

Although data were obtained in only one patient in whom amino acids were given separately from glucose, the findings (Fig. 1) were so striking and confirmatory of so many other observations in the literature that one cannot doubt that they illustrate a universal phenomenon in the utilization of protein nourishment, i.e., that the administration of protein must be synchronous with the administration of carbohydrate (and/or fat) in order to obtain the maximum positive influence on nitrogen balance. This time factor may also be important in the metabolism of carbohydrate given intravenously, in that less sugar seems to be lost in the urine when given simultaneously with amino acids than when given separately. This may be due to the fact that the simultaneous entrance of carbohydrate and amino acids into the metabolic pool enhances the storage or oxidation of carbohydrate, or both. That the administration of amino acids seems to improve the retention of glucose was sug-

gested in previous observations by Lockhart and Elman.[18] In view of the present findings and the suggestive findings by others with oral feedings, as already discussed, this phenomenon should be investigated further.

That the rate with which food nutriments enter the metabolic pool influences the degree of amino acid utilization is shown in the three experiments illustrated in Tables I, II and III. Here again these findings confirm those of others both in humans and in animals during oral feeding. There can be no doubt, therefore, that under certain conditions slow intravenous infusions of amino acids and glucose lead to better utilization of both, particularly on inadequate caloric intakes. From the practical point of view, however, short infusions (through a needle) have been preferred by patients for obvious reasons.

During the past few years, continuous intravenous infusions have been greatly facilitated by the use of indwelling polyvinyl plastic catheters introduced into the vein at the time of operation. The original basis for this technique was the advantage of avoiding repeated venipunctures, particularly in patients with few or very small peripheral veins. Moreover, the flexible tube does not require the rigid immobilization of the arm or leg so necessary when a needle is used. From the present findings, this method of continuous intravenous infusions has another advantage, namely, the better utilization of amino acids.

As to the utilization of glucose, the findings as shown in Figure 1 certainly suggest the advantage of giving amino acids and glucose together. In two of the remaining three experiments, there was a significantly greater loss of glucose during short periods of infusion as compared with the longer periods. However, in the case illustrated in Table II, this difference was absent, although the actual amount of glucose lost during both periods was not very great.

Summary

The existence of two time factors in the metabolism of amino acids given intravenously is shown by nitrogen balance studies in 4 patients given infusions of an inadequate caloric mixture of glucose and amino acids, each patient serving as his own control. The findings indicate a greater utilization of amino acids (1) when glucose was infused at the same time, and (2) when the mixture was infused at a slower rate. These findings confirm observations made by others in humans and in animals with oral feeding.

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Resumen

Factores de tiempo en la utilización de una mezcla de aminoácidos (hidrolizado de proteína) y dextrosa administrada por vía endovenosa

La existencia de dos factores de tiempo en el metabolismo de los aminoácidos administrados por vía endovenosa se ha demostrado por estudios del balance de nitrógeno en 4 pacientes recibiendo infusiones de una mezcla calóricamente inadecuada de glucosa y aminoácidos, cada paciente sirviendo como su propio control. Los hallazgos indicaron una mayor utilización de los aminoácidos (1) cuando la glucosa fué administrada simultáneamente, y (2) cuando la mezcla fué infundida más lentamente. Estos hallazgos confirman observaciones ya hechas por otros—tanto en el hombre como en los animales—con alimentación oral.

Food Sophistication?

"We have started down a long, steep slope of sophistication, processing, bedevilment—call it what you will—the end of which we cannot foresee. Scarcely a single article of diet arrives on our tables unembellished by the technologist's art. Most of the substances employed are as yet enigmatic—we do not know their long-term effects, though some we do know now to be potentially poisonous. Unless the medical profession takes a firm stand, expediency will continue to triumph over caution and common sense, and we may well be faced with irreversible results. Willy nilly we are being made the subject of experiment every day in the week, with the prospect that, sooner or later, one may turn out badly and nobody will be in a position to recognize it for nobody will have met it before. This is really unendurable. It is more than time that our present lethargy and inertia were replaced by an alert and suspicious vigilance and that all proposed and existing food additives were subjected to the sharpest scrutiny. Now that the process of chemical embellishment reaches back to the very soil in which our food is grown, 'if man is,' as the Germans say, 'what he eats,' then synthetic man has arrived, and we may well spend the next generation in medicine trying to unscramble him."
—Editorial. *The Medical Press:* 228: 522, 1952.

The Solitary Eater

"Units in which food is purchased presuppose a family group, and it requires skill to buy economically for one. A study of the subjects' usual choice of food will generally disclose some good dietary practices. Building on these practices rather than presenting an entirely new pattern of eating frequently results in better cooperation."
—M. A. Ohlson, L. Jackson, R. M. Beegle, D. Dunsing, and E. C. Brown. *Journal of the American Dietetic Association* 28: 1143, 1952.

Sad Facts for Sad Sacks

"There is no answer to the problem of these unfortunate patients whose face gets haggard and drawn while their stomach and hips and legs remain gross. There may be some endocrine condition unrecognised by endocrinologists or some lymphatic hypoplasia, but whatever the cause they are doomed to remain like a pyramid, with a little head, and a big base. Diet, massage, baths and all the armament of semiquackery will not help. It is kindest to say so."
—F. Bicknell. *The Medical Press* 228: 493, 1952.

Dietary MODIFICATIONS *of Plasma* CHOLESTEROL *and* PHOSPHOLIPID LEVELS *in* DIABETIC PATIENTS

The Effects of Mixed Diets High in Vegetable Fat

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with the technical assistance of GERTRUDE CAWLEY, MARJORIE COELHO, GEORGE FUKAYAMA, FLORENCE OLSON, AND SADIE SMYRL

As previously reported from this laboratory, the administration of formula diets high in vegetable fat results in a striking fall in the level of plasma cholesterol and phospholipids in patients with a wide variety of disease states, including diabetes.[1] The present study describes the results obtained in a small group of diabetic patients and in one patient with "familial hypercholesterolemia" maintained on a mixed (nonformula) diet, also high in fat content, in which essentially all of the fat was of vegetable origin.

Method

For the past three years, for reasons which will be presented elsewhere, all diabetic patients who are followed in the diabetes clinic of this institution are maintained on diets which contain larger amounts of fat and protein than is common practice. The greater portion of the fat is of animal origin. The composition of these "standard" diabetic diets is shown in Table I.

A group of 70 diabetic patients maintained on such diets were "screened" for levels of plasma lipids, for evidence of peripheral vascular disease, and for evaluation of probable cooperation in the course of a semicontrolled, long-term study. From this group, five were chosen who had slightly or markedly elevated plasma lipid values, who had probable or definite peripheral vascular involvement, and in whom the probability of cooperation seemed good. After initial brief determination of base line values for plasma lipids on the original high "animal lipid diet," these patients were placed on a special diet which differed from the standard diet only in that the fat (and some of the protein) was of vegetable rather than animal origin. The sources of the vege-

TABLE I
Standard Diabetic Diets

Diet number	Approximate calories	Carbohydrate	Protein	Fat	Daily calories
		Gm.	*Gm.*	*Gm.*	
1	1500	135	98	66	1526
2	1800	118	108	101	1813
3	2100	135	119	123	2123
4	2400	143	132	143	2387
5	2700	160	150	163	2707

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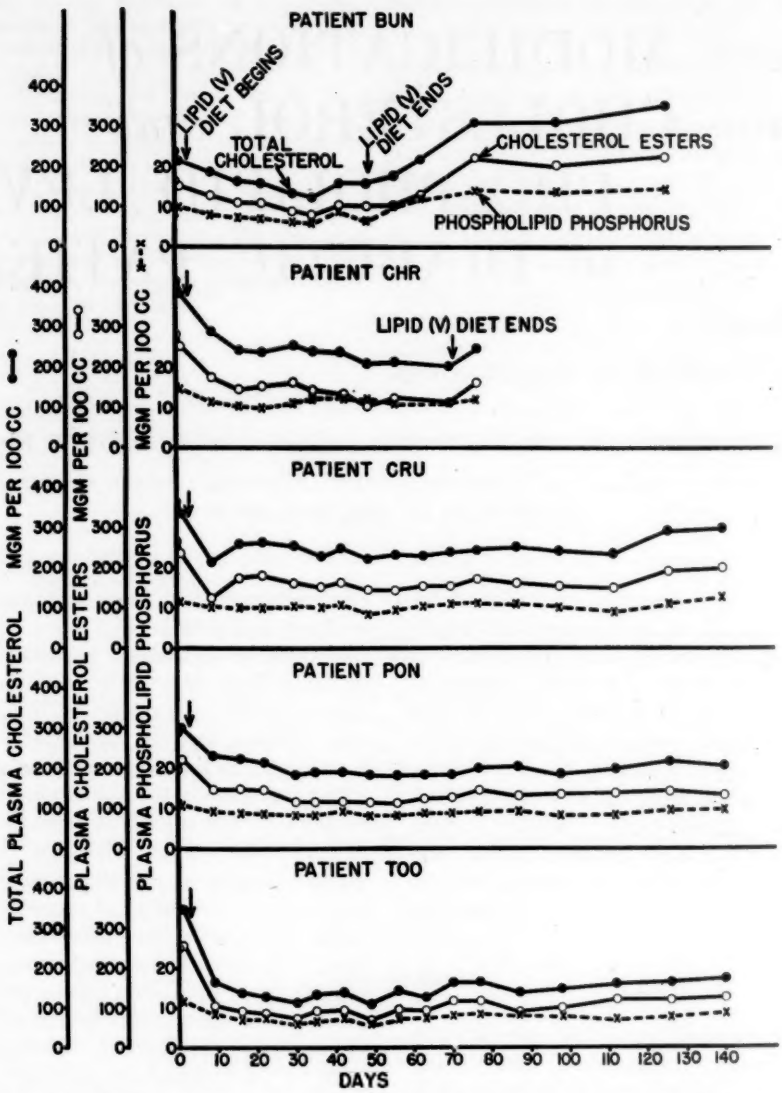

Fig. 1. Plasma lipids in 5 diabetic patients maintained on high protein-fat diets in which the source of the fat was of vegetable rather than animal origin during the greater portion of the study.

table fat for the most part were unsalted nuts and margarine. Insulin administration in a given patient remained nearly constant, and varied from 0 to 56 units of NPH insulin daily.

In Figure 1 are shown the changes in plasma cholesterol and phospholipids in these patients during the study. It will be noted that without exception, a significant fall occurred in a short period of time when the "vegetable lipid diet" was consumed.

After a lapse of seven and ten weeks respectively, patients BUN and CHR returned to their original diets, with a rapid return of

their lipid values toward or above their control values. Patient CRU initially adhered to the vegetable fat diet, but has admitted that for at least ten weeks she has surreptitiously added some milk and meat to the dietary intake.

A similar semicontrolled study was carried out in a patient with "familial hypercholesterolemia." On the mixed high vegetable lipid diet, in the space of thirty days her total cholesterol fell from 420 mg. to 260 mg./100 cc., and a nearly comparable fall occurred in the plasma phospholipid phosphorus.

From the foregoing, it was apparent that a mixed diet containing large amounts of vegetable fat and essentially no animal fat resulted in the same changes in plasma lipids which occurred in patients receiving formula diets, also containing large amounts of vegetable fat. The question, therefore, arose as to whether this change in lipids was referable to the absence of cholesterol and of certain other lipid materials in the vegetable as compared to the animal fat, or whether the fall was referable to a positive effect of some constituent of the vegetable fat, or to some other dietary entity. With this in mind, a young diabetic patient with extensive vascular disease and with marked elevation of plasma lipids was admitted to the metabolic ward for more precise study. After a control period on a "standard" diabetic diet of 1800 calories daily, mixed nuts equivalent to 1600 calories were added to the diet, bringing the total caloric intake to 3400. The laboratory findings in this patient are shown in Figure 2. During the first week on this program, the plasma lipid values rose to 580 mg. per 100 cc., followed by a gradual fall, so that after 35 days on this diet, the total cholesterol was 300 mg. per 100 cc. and the phospholipid phosphorus 12 mg. per 100 cc. The patient was then placed on a vegetable fat formula diet, with a further marked fall in plasma lipids.

Summary and Conclusions

Substitution of fat of vegetable origin for "animal fat" in high protein, high fat, diabetic diets, the total protein, fat, and carbohydrate content remaining unchanged, resulted in a major fall in levels of plasma cholesterol and phospholipids in diabetic patients, and in one

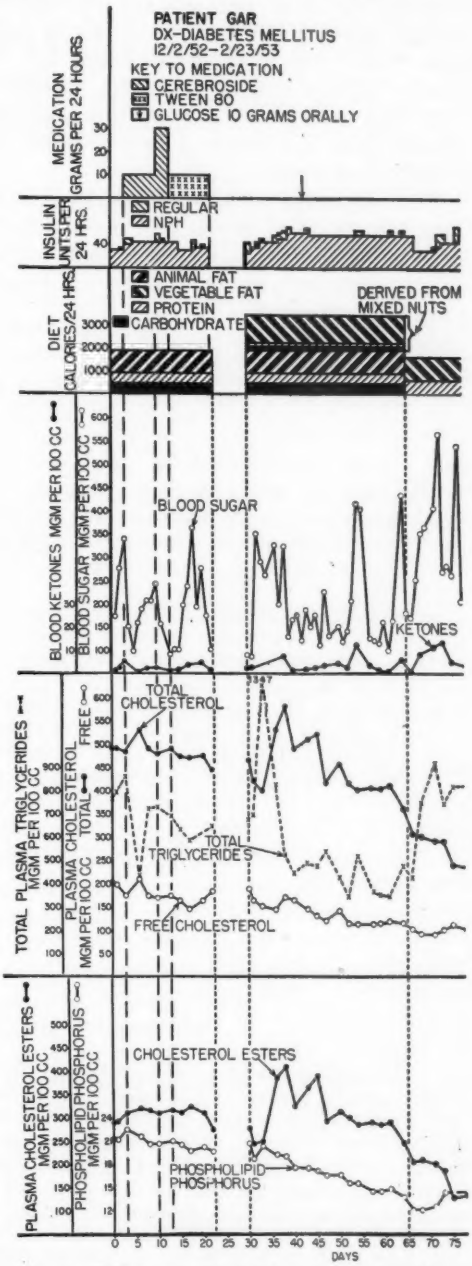

Fig. 2. Effects of added fat and protein of vegetable origin upon the plasma lipids of a diabetic patient maintained on a high animal fat diet.

patient with "familial hypercholesterolemia." In one patient with severe diabetes, the *addition* of 134 Gm. of vegetable fat (as nuts) to a high animal fat "standard" diabetic diet, also resulted in a slow but major fall in plasma lipids. It seems probable, therefore, that the explanation for such changes in plasma lipids lies outside the mere absence of dietary cholesterol.

To further clarify the meaning of these findings, the effects of sterols and phospholipids of vegetable origin upon plasma lipids in patients maintained on high animal fat intake are being evaluated.

ACKNOWLEDGMENT

Grateful acknowledgment is made to Circus Foods, Incorporated, for supplies of nuts used in this study.

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RESUMEN

Modificaciones dietéticas de los niveles de colesterol y fosfolípidos en el plasma de diabéticos. Efectos de dietas mixtas ricas en grasa vegetal

La sustitución de grasa de origen vegetal por "grasa animal" en dietas diabéticas ricas en grasas—el contenido en proteínas totales, grasas e hidratos de carbono quedando lo mismo—resultó en un descenso importante de los niveles de colesterol y fosfolípidos plasmáticos en pacientes diabéticos y en un paciente con "hipercolesterinemia familiar." En un paciente con diabetes severa, la *adición* de 134 grs. de grasa vegetal (en forma de nueces) a una dieta diabética "standard" rica en grasa animal, resultó también en un lento pero importante descenso de los lípidos del plasma. Parece, pues, probable que dichos cambios en los lípidos del plasma tienen que explicarse de otro modo que no por la mera ausencia de colesterol dietético.

Para esclarecer mejor el significado de estos hallazgos, se están analizando los efectos de esteroles y fosfolípidos de origen vegetal sobre los lípidos plasmáticos en pacientes sometidos a una dieta rica en grasa animal.

"The Fat Organ"

"In passing, it is amusing to play with the theory that fat is not a store of food but is an active organ—the fat organ—of the body, which is necessary for dealing with carbohydrates. When the diet contains large amounts of carbohydrate the fat organ, having little work, shrinks. The obese patient is one whose fat organ is degenerate, and it therefore has to grow large to deal with the same amounts of carbohydrate that a small, healthy fat organ can handle. On this theory the obese patient dies young not because of his fat, but because he has a constitutional degeneration which though it shows itself so obviously in his fat organ is equally present in his heart, blood vessels, joints, etc. There are no figures to show that dieting has ever prolonged life: that the fat do not die early whether they are fat or thin through dieting, though of course it would seem probable that the degenerate organs of the obese will fail more tardily if the fat organ ceases to be a heavy burden on them."

—F. Bicknell. *The Medical Press* 228: 491–492, 1952.

INTRAVENOUS *TREATMENT OF PERNICIOUS ANEMIA WITH* VITAMIN B_{12}

By LEO M. MEYER, M.D.,* ROBERT McINERNY, M.D.,† AND NORTON D. RITZ, M.D.‡

NUMEROUS observers have reported successful hematologic and clinical remissions in pernicious anemia in relapse following intramuscular injections of vitamin B_{12}, and the oral administration of this vitamin alone, or with normal gastric juice, extracts of hog duodenal mucosa, or folic acid. The only report bearing on intravenous therapy is by Gardner *et al.*[1] who administered beef muscle extract showing vitamin B_{12} activity (equivalent to 0.35 to 9.0 μg.) intravenously for 10 days and noted a hematologic effect which was less than that observed after the daily intramuscular injection of 1.0 μg. of crystalline vitamin B_{12}.

The present study was undertaken to study the effect of daily intravenous injections of crystalline vitamin B_{12} to 5 patients with pernicious anemia in relapse. Four of them received 1.0 μg. daily for 13 to 33 days. Two of the patients were subsequently treated with 7.0 μg. intravenously, weekly, for 28 to 63 days. The fifth case was treated with 0.5 μg. daily for 26 days. Prior to treatment each of the patients showed hyperchromic macrocytic anemia, histamine-fast achlorhydria, and megaloblastic bone marrow. Roentgen examinations of the gastrointestinal tract, urinalyses, and blood chemistry determinations disclosed no abnormalities. Hemoglobin and erythrocyte determinations were made three times a week, leukocyte counts once a week, and reticulocyte counts daily. Maximal reticulocyte peaks and anticipated red blood cell levels at 15 days were calculated from the formulae of Isaacs and Friedman[2] and Ungley,[3] respectively. None of the patients showed evidence of chronic pulmonary or heart disease.

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RESULTS

All of the patients showed a satisfactory clinical response as evidenced by increase in appetite, sense of well-being, and strength. No untoward reactions were experienced following injections. In case A. S., bronchopneumonia developed during the second week of therapy, for which he was treated with penicillin intramuscularly. This episode may account for the suboptimal reticulocyte peak and slightly lower erythrocyte level at 15 days. More patients will have to be treated with 0.5 μg of vitamin B_{12} intravenously, daily, to compare the results with those obtained with the larger dose. In the group receiving 1.0 μg. daily, the reticulocyte response was suboptimal in 2 cases and reached anticipated levels in the other instances. Erythrocyte counts at the end of 15 days in all patients were higher than expected. In cases treated for 41 and 87 days, polycythemic levels of 5.80 and 5.91 million per cu. mm., respectively, were attained. Hemoglobin levels, although elevated, were slightly hypochromic, probably reflecting the rapid red blood cell regeneration.

TABLE I.

Hematologic Data on Patients with Pernicious Anemia in Relapse Treated with 1 μg. of Vitamin B_{12} Intravenously Daily

Patient	Dose B_{12}	Time	Initial Hb.	Final Hb.	Initial RBC $\times 10^6$	Final RBC $\times 10^6$	Retics. peak/day	Antic. peak retic.	Predicted RBC: Observed RBC $\times 10^6$ at 15 days	Predicted RBC: Days of observation
	μg.		Gm.	Gm.			%	%		
A. S.	0.5/day	26 days	6.0	9.0	1.38	2.65	19.7/8	30.5	2.43/2.20	26
W. S.	1.0/day	33 days	5.0	11.5	1.16	4.06	33.3/8	42.0	2.50/3.50	33
I. C.	1.0/day	33 days	7.0	14.2	1.70	4.65	27.6/6	29.0	2.99/3.38	33
J. H.	1.0/day	13 days	9.5	16.5	2.50	5.80	6.9/6	15.0	3.74/4.35	41
	7.0/week	4 weeks								
M. G.	1.0/day	24 days	6.2	16.0	1.46	5.91	28.6/6	28.7	2.76/5.03	87
	7.0/week	9 weeks								

No neurologic changes were observed prior to or following vitamin B_{12} therapy.

Discussion

Erythremic levels in pernicious anemia following treatment are rare.[4] Personal experience of one of us (LMM) with more than 300 cases of pernicious anemia treated with various agents disclosed only one instance in which the erythrocytes rose above 5.8 million per cu. mm. This patient was treated with animal protein factor and vitamin B_{12}. Previous observations demonstrated that daily intramuscular injections of 1.0 μg. of vitamin B_{12} to patients with pernicious anemia in relapse was followed by suboptimal reticulocytosis and unsatisfactory hematologic levels after 2 months of treatment.[5] In contradistinction, the present group treated with 1.0 μg of vitamin B_{12} intravenously, daily, showed a better than anticipated increase of red blood cells in all 4 cases. The failure to achieve optimal reticulocyte levels has been repeatedly observed where hematologic remissions were otherwise satisfactory.[6,7] Whether the immediate availability of vitamin B_{12} in the bloodstream results in the production of more "serum hematopoietic factor" to antagonize folinic acid inhibitor,[8] or the presence of the cobalt radical of the vitamin B_{12} induces greater erythropoiesis than by intramuscular or oral routes, is open to speculation. The mechanisms whereby cobalt increases red cell production by interference with the transport of oxygen in the erythroid cells of the bone marrow have been variously ascribed to binding of sulfhydryl groups[9] or alterations in the catalase molecule in which the cobalt atom replaces an iron atom, making the latter available for additional hemoglobin synthesis.[10] Berk and coworkers demonstrated an erythropoietic effect in patients with and without anemia following oral administration of cobalt.[11] No case of pernicious anemia in relapse was included in their series.

Conclusions

Daily intravenous administration of 0.5 or 1.0 μg. of vitamin B_{12} to 5 patients with pernicious anemia in relapse induced a satisfactory clinical remission.

Erythrocyte regeneration was satisfactory in 1 case (receiving 0.5 μg. per day) and greater than anticipated in 4 cases (receiving 1.0 μg. per day).

Erythremic levels were attained in 2 patients treated for 41 and 87 days with 1.0 μg. of vitamin B_{12} daily.

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RESUMEN

Tratamiento endovenoso de la anemia perniciosa con Vitamina B_{12}

La administración endovenosa de 0,5 u 1,0 microgramo por día de vitamina B_{12} a 5 pacientes con anemia perniciosa recidiva logró una remisión clínica satisfactoria.

La regeneración de los eritrocitos fué satisfactoria en un caso (recibiendo 0,5 microgramo por día) y mayor de lo que se había anticipado en 4 casos (recibiendo 1,0 microgramo por día).

Los niveles eritrémicos se consiguieron en 2 pacientes tratados durante períodos de 41 y 87 días con 1,0 microgramo por día de vitamina B_{12}.

The Use of ORAL FAT PREPARATIONS *in Medicine*

By ARTHUR GROLLMAN, M.D., PH.D., F.A.C.P.

THE IMPORTANCE of supplying the sick patient with an adequate caloric intake is generally acknowledged and has been receiving increased attention in recent years with the recognition of the value of a normal nutritional state in effecting recovery from illness. The sick individual often loses weight because of inability to consume an adequate caloric diet, which in turn exerts a deleterious effect on his recovery. The inability of such patients to consume the large amounts of the ordinary foodstuffs tolerated by the normal individual has long presented the physician with the problem of obtaining foods high in caloric value in a form which can be easily administered and tolerated by the patient. For this reason attention has been directed recently to the elaboration of formulae of various sorts in which fat, because of its high caloric value (9.3 calories per gram), has received special attention. In addition to the value of such preparations because of their caloric content, they have also received attention as a source of material which is completely utilized by the organism and which, being free of salts and of nitrogen, is useful in patients with acute renal failure. The present paper describes these fat emulsions which are now available commercially and which have found application in clinical practice.

FAT METABOLISM

The superiority of fat over other foodstuffs because of its high caloric equivalence has long been known. The sparing action of carbohydrate on protein catabolism and the essential nature of carbohydrate in metabolic processes have also long been recognized. However, it has only recently been realized that the efficiency of energy utilization of diets equal in their protein and energy content increases with their increasing dietary fat content.[1] The combination of fat and carbohydrate accordingly affords a unique combination which furnishes an easily assimilable source of calories, represses endogenous protein catabolism to a minimum, and induces an optimal efficiency in the utilization of administered protein. By adding a sufficient quantity of fat to a diet containing only marginal quantities of protein it is possible to increase the efficiency of utilization of the latter. Nitrogen and potassium deficits due to calorically inadequate diets may also be abolished by supplementary fat feedings.[2]

A certain amount of fat in the diet usually adds to its palatability. Excessive quantities are usually rejected, except by certain peoples (e.g., the Eskimo). Fat also inhibits gastric peristalsis and delays the emptying time of the stomach. As a consequence, it may induce bloating, a feeling of fullness, and epigastric distress. For this reason, when given as a supplementary feeding, fat should not be administered with meals, but preferably between meals and in the evening. The only absolute contraindication to the use of fat emulsions appears to be the presence of biliary tract calculi or pyloric obstruction with retention.

AVAILABLE FAT-CARBOHYDRATE EMULSIONS

Cream has long been utilized as a naturally occurring source of fat. Synthetic prepara-

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tions of fat and carbohydrate were first utilized clinically in the management of patients with acute renal failure for whom a protein-free diet was desired. Borst[3] in 1948 suggested the use of such diets consisting principally of sugar and butter. The unpalatability of such concoctions led Bull, Joekes, and Lowe[4] to utilize a simple water emulsion containing peanut oil and glucose. Such mixtures may be readily prepared in the laboratory and when supplemented by vitamins, proteins, etc., serve as a convenient foodstuff in experimental studies in which the forced feeding of a diet of constant and known composition is required.[5]

The commercially available fat-carbohydrate emulsions contain 40 and 50 per cent vegetable oil (peanut, coconut) and 10 per cent glucose in water to which is added an emulsifying agent, an antioxidant and a preservative. Two commercial products are marketed: Lipomul-Oral® (Upjohn) and Ediol® (Schenley). The former is flavored with chocolate in order to mask its taste; the latter requires no flavoring agent and has a pleasant taste faintly suggestive of vanilla. The nauseating "fatty" taste of oil is dissipated by the smallness of the particles (1 micron or less) in which it is dispersed. These small particles coalesce when subjected to the acidity of the stomach contents, but this does not interfere with their efficient absorption, since even gross fat is readily assimilated even when administered in large amounts. However, incubation of one of the commercially available emulsions (Ediol®) for 48 hours in 0.1 *N* hydrochloric acid does not break the emulsion. Examination of the material obtained by gastric aspiration up to four hours after administration also reveals the emulsion to be unbroken.

The available fat-carbohydrate emulsions are well tolerated even in relatively high doses. Thus Van Itallie and his coworkers[2] gave normal volunteer subjects as much as 250 to 500 ml. of the preparation providing 1000 to 2200 calories per day; many patients tolerate readily 250 ml. in addition to their usual diet. Even when given in such large amounts, fat balance studies demonstrated that the fat was well assimilated and there were only insignificant increases in the fecal fat content.[2]

Methods of Administration

The fat-carbohydrate emulsions may be administered in various ways, depending on the purpose for which they are being used. They may be given undiluted in doses varying from 15 to 120 ml. at intervals of several hours. They may also be administered, if necessary, by intragastric drip through a nasal tube. The available preparations mix well with water, milk, or fruit juices, and are best administered in this way when used in conjunction with a regular diet. The caloric equivalent of Lipomul-Oral® is 4 calories per ml.; that of Ediol® about 5 calories per ml. Because of these high caloric equivalences, a high caloric diet may be supplied in smaller bulk than is otherwise possible.

Fat emulsions suitable for intravenous administration are also under investigation but are not available commercially.

Experimental and Clinical Uses

Fat-carbohydrate emulsions have been used for a variety of experimental and clinical purposes. They serve as a basis for diets which must be administered by stomach tube in experimental animals.[5] Because of their negligible salt content they are ideal for the maintenance of the nephrectomized animal.[6] By their use one can maintain such animals for a much more prolonged period than is otherwise possible without resort to such artificial measures as peritoneal lavage or the artificial kidney.[7] For other experimental studies where a diet of known composition is desired, the fat-carbohydrate emulsions may be modified by the addition of protein, salts, vitamins, etc., as are indicated.[6]

Clinically, one of the first applications for the use of fat-carbohydrate emulsions has been in the management of patients suffering from acute renal failure.[3,4,7] In such patients it is desirable to administer food of sufficient caloric value to depress the endogenous protein catabolism to a minimum. Such food must also be free of protein and salts. Fat-carbohydrate emulsions have served admirably for this purpose. Approximately 250 ml. of the

emulsion will furnish 1000 calories, which may be further supplemented by a sufficient amount of glucose in water administered orally or intravenously to furnish the water requirement of the patient. By this means, patients with complete anuria have been kept in good condition with a slowly rising nonprotein-nitrogen level of the blood for periods of 10 to 30 days.[4,7]

For patients who are underweight, supplemental feedings of commercially available fat-carbohydrate emulsions have resulted in satisfactory weight gains. For this purpose, the emulsions are administered in doses of 30 to 120 ml., diluted if desired in a glass of milk or water between meals and before retiring.

There are many clinical conditions in which a liquid supplemental feeding of high caloric value is desirable. Most illnesses are characterized by anorexia, which leads to a deficient diet, weight loss, and a negative nitrogen balance. The resulting undernutrition in turn accentuates the anorexia, thus leading to a vicious cycle. In many patients—for example, those suffering from febrile disorders, hyperthyroidism, or burns, fractures, surgical operations, etc.—there is also an increased rate of endogenous protein catabolism which can be counteracted only by the ingestion of a caloric intake higher than the normal basal requirement.

The effectiveness of fat emulsions in the dietary management of severely burned patients has been demonstrated by Levenson, Lounds, and Morris,[8] who were able to maintain their patients in positive nitrogen balance by the use of a liquid diet, 25 per cent of the calories of which were supplied by emulsified fat. These authors have demonstrated the capacity of such alimentation to maintain the patient in a good state of nutrition, which in turn contributes to good healing and the avoidance of potentially fatal complications.

In surgical patients with obstructing lesions of the upper gastrointestinal tract (mouth, esophagus, and stomach) only a liquid diet can usually be consumed. For such cases, Goldberg, Stein, and Meyer[9] found that the administration of 400 Gm. of fat daily in the form of a 40 per cent fat emulsion was well tolerated and absorbed and permitted a positive nitrogen balance with a moderate protein high caloric intake. Although undesirable side-effects—nausea, vomiting, diarrhea, and constipation—occurred in about half of their 76 patients, these symptoms were mild and transitory and did not require cessation of the therapy.

The importance of maintaining a good state of nutrition in the prevention as well as in the management of the tuberculous patient has long been recognized. Dailey[10] has used dietary supplements containing 2 oz. of fat-carbohydrate emulsion homogenized with milk and milk protein twice daily and at bedtime in 63 patients with pulmonary tuberculosis. In patients in whom the disease was static, this regimen resulted in an increased rate of weight gain; in those with progressive disease, the rate of weight loss was reduced.

Nutritional care also constitutes an important aspect in the treatment of poliomyelitis. To spare body protein and enhance the utilization of ingested protein, oral fat emulsions have been found of value by Boines[11] in this condition. Likewise in children with rheumatic fever, the inclusion of fat emulsions and protein concentrates in the diet has been found effective in offsetting the catabolic effects of cortisone and corticotropin therapy.[12]

The above-cited publications exemplify some of the clinical conditions in which the use of fat emulsions has proved of value. They may be used with advantage in many other conditions. Restoration or maintenance of body weight, a positive nitrogen balance, and an adequate caloric mineral and vitamin intake can be achieved by the use of liquid diets which may be readily prepared and which are well tolerated and assimilated.[13] In chronic illnesses, in the preparation of patients for surgery, and in the management of patients with chronic or acute renal failure in whom control of the protein and salt intake is essential without too great restriction of the caloric intake, the use of fat emulsions as a dietary adjunct is of greatest value.

Summary

Fat is an important constituent of the diet. Its uniquely high caloric value renders it an

ideal substance for supplying in a ready assimilable liquid form an adequate amount of calories which permits optimal utilization of protein. The commercially available emulsions of fat and carbohydrate have been used to advantage in a variety of clinical conditions: acute renal failure, burns, surgical conditions requiring a liquid diet, tuberculosis, poliomyelitis, etc. They are also effective when used as supplementary feedings in underweight or malnourished individuals and are useful in experimental laboratory or clinical studies in which a diet of known composition and high caloric value is desired.

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Resumen

El uso de las preparaciones orales de grasas en la medicina

Las grasas constituyen un factor importante de la dieta. Por su altísimo valor calórico las grasas son substancias ideales para la provisión, en forma líquida y facilmente asimilable, de una cantidad adecuada de calorías, permitiendo la utilización óptima de la proteína. Los hoy disponibles preparados comerciales de emulsiones de grasas e hidratos de carbono se han empleado con provecho en una variedad de condiciones clínicas: claudicación renal aguda, quemaduras, condiciones quirúrgicas que requieren una dieta líquida, tuberculosis, poliomielitis, etc. Asimismo son efectivos cuando se los emplea como suplementos alimenticios en individuos delgados o malnutridos, y son útiles en experiencias de laboratorio o clínicas en que se quiere emplear un régimen de composición conocida y alto valor calórico.

Disease and Divinity

"It seems to me that the disease is no more divine than any other. It has a natural cause, just as other diseases have. Men think it divine merely because they do not understand it. But if they called everything divine which they do not understand, why, there would be no end of divine things."

—Unknown Hippocratic physician, Fifth Century B.C.; cited by B. Farrington in *Greek Science; Its Meaning for Us* (*Thales to Aristotle*), Penguin Books, Harmondsworth, England, 1948.

Editorial

Ascorbic Acid, Stress, and the Adrenal Gland

In 1753, just two hundred years ago, James Lind[1] wrote his famous *Treatise of the Scurvy* which pointed the way to the discovery of ascorbic acid. His writings also perpetuated the concept that ". . . cold, damp, fatigue, and hard work precipitated scurvy." The modern view, stemming from the concepts of Selye and the observations of Sayers and Sayers,[2] inclines to the belief that ascorbic acid requirements for man are increased as a result of a variety of stressful situations which include burns, severe injuries, operations, infections, and rheumatic diseases.

Between 1941 and 1947, Lund and Levenson and their colleagues[3,4] studied ascorbic acid in the urine and plasma of patients subjected to surgical stresses of one kind or another. They found that both plasma levels and urinary output of ascorbic acid dropped to low values in the postoperative period, despite treatment with very high doses of ascorbic acid. They explained these findings on the basis of increased utilization of ascorbic acid.

At about the same time, Sayers and Sayers,[2] working with rats, demonstrated that adrenal ascorbic acid and adrenal cholesterol decreased when the animals were stressed or when their adrenal cortices were stimulated with corticotropin (ACTH). These observations on rats led Levenson and Lund to postulate that the increased demand for, and utilization of, ascorbic acid was related to increased consumption of the vitamin by the adrenal gland.

Since then there has been a general acceptance of Levenson and Lund's observations of, and speculations on, ascorbic acid requirements in states of "damage" or stress. Thus, there exists at present a strong belief, among surgeons and physicians, that large amounts of ascorbic acid are consumed during illness by the adrenal gland in its synthesis of cortical hormones from cholesterol. Conversely, many accept the thesis that adrenal activity will be sharply reduced when ascorbic acid supplies are curtailed. They believe that patients with low plasma levels of ascorbic acid, or with inadequate supplies of ascorbic acid, may develop adrenal insufficiency when they are stressed by surgery or illness. These concepts have been tested experimentally during the past few years by a number of investigators and are now known to be erroneous.

In the light of data now at hand, our ideas of the interrelationships between ascorbic acid metabolism and adrenocortical activity need reorientation, at least with regard to guinea pigs, monkeys, and man, who, unlike the rat, do not synthesize ascorbic acid in their adrenals. Clayton and Prunty[5] and Nadel and Schneider[6] found an increased excretion of urinary 17-ketosteroids, or urinary formaldehydogenic substances by scorbutic guinea pigs, and Long[7] noted that the adrenals of scorbutic guinea pigs could respond normally to stimulation with corticotropin. Observations on adrenal activity in patients ill with classical scurvy[8,9,10] indicate that the adrenal cortex functions normally in the face of gross ascorbic acid depletion, since 17-ketosteroid excretion was normal and the adrenal glands responded in a normal manner to stimulation

by corticotropin. The precise studies by May and his colleagues on scorbutic monkeys[11] indicate clearly that the function of the adrenal cortex bears little, if any, relationship to overall ascorbic acid requirements in man.

May *et al.* studied the eosinophils, urinary 17-ketosteroid output, and the ascorbic acid content of the adrenal glands in 18 monkeys in whom scurvy or ascorbic acid deficiency was produced by a diet completely free of ascorbic acid. The data were compared with observations from control animals, some of whom had had their adrenal glands removed. In the deficient or scorbutic monkeys the ascorbic acid in the adrenals—as in other tissues—fell to low levels (i.e. from 50 to 3 mg. per 100 Gm. of adrenal gland). Despite this wasting of tissue and glandular ascorbic acid, the 17-ketosteroid output remained normal and even increased in some of the animals. Whenever the scorbutic animals were stimulated with corticotropin there was a marked increase in 17-ketosteroid excretion. The eosinophils in the monkeys dropped to very low levels during depletion, and with the advent of scurvy the level was zero, suggestive of adrenal hyperactivity. These experiments conclusively demonstrate that the adrenal cortex functions normally during scurvy or severe ascorbic acid depletion, and can respond in a normal manner to repeated stimuli by corticotropin. Therefore, the adrenal gland cannot consume much ascorbic acid in the synthesis of cortical hormones.

As far as we are aware, there are no reports in the literature on the coexistence of scurvy and Cushing's syndrome. In my experience, patients with Cushing's syndrome have normal ascorbic acid levels in their blood and no evidence of scurvy. The Clinical Sections on Endocrinology at the Mayo Clinic have seen over 100 cases of patients with Cushing's syndrome, and Dr. E. H. Rynearson,[12] reporting on behalf of his colleagues, writes as follows: "First, we have not observed frank scurvy in patients with Cushing's syndrome; second, we have administered large doses of ascorbic acid to a number of patients with Cushing's syndrome without any apparent modification of the condition; and third, a few determinations of blood ascorbic acid have not revealed any significant abnormalities."

Since activity of the adrenal cortex of man does not seem to require ascorbic acid for synthesis of cortical hormones and cannot use up large amounts of ascorbic acid in its production, how can we explain the disappearance, or retention, of ascorbic acid in the damaged patients studied by Levenson and Lund? The best explanation is given by Lauber and Rosenfeld[13] and Bartlett *et al.*[14] They studied the ascorbic acid content of healing wounds and scars produced experimentally in healthy and in scorbutic guinea pigs. They showed that ascorbic acid was mobilized from the tissues and organs of the body and selectively concentrated in the traumatized area. Thus the plasma and urinary levels may be expected to be low. Whether ascorbic acid does any good there is another matter and must remain a subject for speculation until further data are at hand.

—Robert M. Kark, M.R.C.P. (Lond.)

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Dietotherapy

** The Dietotherapy section, usually authored by Corinne H. Robinson, is in this issue given over to a special article on diet in diabetes by Doris Johnson, Ph.D., Director of Dietetics, Grace-New Haven Community Hospital and Assistant Professor of Public Health (Nutrition), Yale School of Medicine*

PLANNING THE MODERN DIABETIC DIET

MODERN nutritional concepts stress that therapeutic diets are modifications of the normal diet.[1] This applies to the diabetic patient as well as to others in whom dietotherapy is an essential part of clinical management. No longer need the diabetic patient feel that his diet is a handicap or that he requires many specially prepared foods which set him apart from the rest of the family. Today the diabetic patient builds his diet upon the same basic foods required for adequate nutrition as does the normal individual.

Since the nutritional management of the diabetic patient is of necessity an individual matter, it is imperative to plan a diet to fit each patient's need. The total caloric requirement of the patient should be the first consideration. Caloric needs are based on the patient's "ideal" weight and activity. Tables of height and body structure as related to age are available[2] and may be used to determine the patient's "ideal" weight. The caloric allowance for the moderately active normal adult is approximately 20 cal. per pound of so-called ideal body weight.[3]

CALCULATIONS

The caloric allowance for the moderately active diabetic patient is kept somewhat below this amount, usually at about 15 cal. per pound of ideal body weight. This is advisable since weight reduction is often necessary for the diabetic and it also serves as a means of keeping the metabolic process more nearly within the capabilities of the patient. Thus a moderately active patient whose ideal weight is 120 lb. would require approximately 1800 cal. per day.

After the caloric requirement has been determined, the protein allowance for the patient may then be planned. Again, the ideal weight of the patient is used as the basis for calculation. The protein allowance for the diabetic patient is, in general, the same as that for the normal individual. The protein allowance has been established at $^1/_2$ to $^2/_3$ Gm. per pound of ideal body weight per day.[3] Therefore the diabetic patient whose ideal weight is 120 lb. should receive approximately 60 to 80 Gm. of protein per day.

The carbohydrate allowance of the diet is determined by taking 40 to 60 per cent of the nonprotein calories as carbohydrate. In the example previously cited, this would make the carbohydrate of the diet 185 Gm.

1800 (total cal.) − 320 (protein cal.: 80 Gm. × 4 cal./Gm.) = 1480 cal.
50% of 1480 cal. = 740 cal.
740 cal. ÷ 4 cal./Gm. = 185 Gm. carbohydrate

This carbohydrate allowance will provide for a palatable and varied diet for the diabetic patient. Diabetic diets should seldom be prescribed to contain less than 150 Gm. of carbohydrate per day. At lower levels of carbohydrate than this it is difficult, if not

almost impossible, to plan a nutritionally adequate diet which will still be interesting and palatable to the patient and which he will be more likely to follow. From 150 to 200 Gm. of carbohydrate per day are required for an adequate intake of essential foods to meet the established nutritional needs of an individual.

The fat allowance of the diet is calculated from the remaining nonprotein calories. In the example given this is 82 Gm. Since the diet prescription is always written to the nearest 5, the fat prescription will be 80 Gm.

740 cal. ÷ 9 cal./Gm. = 82 Gm.

The final diet prescription should be given in the order: protein, fat, and carbohydrate, and will, in the example given, now read 80-80-185. This order is preferred since most tables of food composition are given in this sequence.

The physician has a further responsibility in determining the patient's diet prescription. He must also specify the division of the *carbohydrate* among the three meals of the day and any between-meal feedings deemed necessary. This again is an individual matter for each patient and must be determined by the physician accordingly, based on the type of insulin used and the patient's response to treatment. It is essential that the division of the carbohydrate of the diet prescription be written as a part of the diet order. As an example, the above order might be written 80-80-185 (35-65-75-10), indicating that the patient was to have 35 Gm. of carbohydrate for breakfast, 65 Gm. for lunch, 75 Gm. for dinner, and 10 Gm. of carbohydrate as a bed-time feeding.

A diet order such as that used in the example will meet the nutritional allowances for our hypothetical patient. The basic diet for the average person in health supplies approximately 75 Gm. protein, 77 Gm. fat, and 170 Gm. carbohydrate.[1] Thus all the essential foods may be supplied in the diabetic diet. It is important, however, that under ordinary circumstances the diet prescription for a diabetic patient include not less than these amounts of protein, fat, and carbohydrate. If a diet lower in calories than the example cited is necessary, care must be taken to see that the prescription is such that the diet will be nutritionally adequate. A 1200 calorie diet can, by careful planning, be made nutritionally adequate. The reduction in calories will be achieved by restriction of fat and carbohydrate. Such a diet supplies approximately 70 Gm. protein, 55 Gm. fat, and 110 Gm. carbohydrate. It is essential that the protein of the diet be not less than the minimum allowance for adequate nutrition. A 1200 calorie diet naturally will not have the variety of selection of foods that the higher caloric diet will have.

The practice of using a preplanned diet prescription for every diabetic patient is not to be condoned. Each diabetic patient must have a diet prescription, just as he receives his individualized prescription for drugs, to meet his particular needs. Besides meeting the physiological requirements of the patient the diet prescription must also meet the social and economic needs of the patient. To give the patient a stereotyped diet, with no consideration for each of these factors, is to defeat the purpose of the diet, since it will not be followed.

The translation of the diet prescription into foods is an extremely important part of planning the diabetic diet.

The Diabetic Diet

A procedure for the planning of diabetic diets was proposed in 1950[4] which has not only the merit of requiring little time to plan a diet but of being simple enough to be readily taught to the majority of patients. It has the further advantage of providing a standardized method for planning the diabetic diet and a classification of foods which may be used throughout the country. This will greatly reduce the confusion which has arisen among patients and doctors alike as to which set of food values to use in planning the diabetic diet. This exchange system was the result of the work of a committee composed of representatives of the American Dietetic Association, the American Diabetes Association, and the Diabetes Branch, United States Public Health Service. The recommendations of this committee were accepted by the represented as-

TABLE I
Composition of Food Exchanges

List	*Food*	*Measures*	*Gm.*	*P*	*F*	*C*	*Cal.*
1	Milk Exchanges	1/2 pt.	240	8	10	12	170
2a	Vegetable Exchanges	As desired	...	...	...	...	...
2b	Vegetable Exchanges	1/2 cup	100	2	...	7	36
3	Fruit Exchanges	Varies	...	...	...	10	40
4	Bread Exchanges	Varies	...	2	...	15	68
5	Meat Exchanges	1 oz.	30	7	5	...	73
6	Fat Exchanges	1 tsp.	5	...	5	...	45

sociations, and the material is available both for the physician and for the patient.[5]

In the proposed systems the foods to be used are classified into six groups called "exchanges." These exchange groups include milk, meat, fruits, vegetables, bread, and fat. Thus only six sets of food composition figures need be known (Table I). The foods included in each exchange group are equivalent as far as proximate composition is concerned and may therefore be substituted one for another (Table II).

The protein, fat, and carbohydrate of the diet prescription are divided into the six exchange groups to form a basic daily food plan (Table III). In doing this, the foods necessary to normal nutrition must be included in adequate amounts.[1] Thus three cups of milk, at least two servings of fruit, two servings of vegetables besides potato, an egg, four ounces of meat or its equivalent, and adequate amounts of whole grain or enriched cereal and fortified margarine or butter should be included in the daily diet plan.

With such a daily diet plan and a list of the foods included in the exchange groups, the patient may be taught how to substitute specific foods into the plan to form the meals he may have each day (Table IV). In this manner the diabetic patient may have a diet with considerable variation in it. He must be taught, however, to select these foods wisely so that he will include the foods necessary for normal nutrition. Emphasis should be placed on including at least one good source of ascorbic acid each day.

Practical Points

In planning a diet for a diabetic patient the physician should discuss with him his food habits and racial or religious customs which may influence his acceptance of certain foods. His hours of work, whether or not he carries a lunch or eats in a restaurant, and his economic status will be other factors which may influence the patient's willingness to accept the diet plan given him. The diet plan must be worked out with the patient so that he will be able to apply it to his way of living. It should be obvious that to give a patient a sheet of paper on which is printed a standard diet is not the answer to his dietary problem. The procedure for calculating diabetic diets presented here is not time consuming and the busy physician who does not have available the services of a dietitian should be able to take the time to plan the diet for each patient so that it will be practical. Experience has shown that if this is not done the patient will not follow the diet and gross errors will result. Moreover, dietary inadequacies may occur which can further complicate the picture.

The modern diabetic diet need not be weighed. Measurement by measuring spoons and cups and by average portions, as in the case of the fruit and bread exchanges, is sufficiently accurate for all practical purposes. The variation in the proximate composition of foods is such that to weigh them by grams implies an accuracy which may not be present.

In looking over the list of food exchanges, it will be observed that types of foods included are such that a wide selection of foods is offered. These foods may be used as is or included in recipes to make many other combinations. The diabetic patient need not be made to feel that he must have so-called "dietetic" foods in order to have an interesting and varied diet. These specialty foods are

TABLE II
Exchange Lists

List 1. Milk Exchanges

Carb.—12 Gm., Protein—8 Gm., Fat—10 Gm., Calories 170

	Meas.	Gm.
* Milk, whole	1 cup	240
Milk, evaporated	1/2 cup	120
* Milk, powdered	1/4 cup	35
* Buttermilk	1 cup	240

* Add 2 fat exchanges if fat free.

List 2. Vegetable Exchanges

A.—These vegetables may be used as desired in ordinary amounts. Carbohydrates and Calories negligible.

Asparagus	"Greens"	Lettuce
Broccoli	Beet	Mushrooms
Brussels Sprouts	Chard	Okra
Cabbage	Collard	Pepper
Cauliflower	Dandelion	Radishes
Celery	Kale	Rhubarb
Chicory	Mustard	Sauerkraut
Cucumbers	Spinach	String Beans, young
Escarole	Turnip	Summer Squash
Eggplant		Tomatoes

B.—Vegetables: 1 serving equals 1/2 cup equals 100 Gm.

Carb.—7 Gm., Protein—2 Gm., Calories—36

Beets	Peas, green	Squash, winter
Carrots	Pumpkin	Turnip
Onions	Rutabaga	

List 3. Fruit Exchanges

Carbohydrate—10 Gm., Calories—40

	Measure	Gm.
Apple	1 sm. (2 in. diam.)	80
Applesauce	1/2 cup	100
Apricots, fresh	2 medium	100
Apricots, dried	4 halves	20
Banana	1/2 small	50
Berries: Straw., Rasp., Black	1 cup	150
Blueberries	2/3 cup	100
Canteloupe	1/4 (6 in. diam.)	200
Cherries	10 large	75
Dates	2	15
Figs, fresh	2 large	50
Figs, dried	1 small	15
Grapefruit	1/2 small	125
Grapefruit Juice	1/2 cup	100
Grapes	12	75
Grape Juice	1/4 cup	60
Honeydew Melon	1/8 (7 in. diam.)	150
Mango	1/2 small	70
Orange	1 small	100
Orange Juice	1/3 cup	100
Papaya	1/3 medium	100
Peach	1 medium	100
Pear	1 small	100
Pineapple	1/2 cup	80
Pineapple Juice	1/3 cup	80
Plums	2 medium	100
Prunes, dried	2 medium	25
Raisins	2 tbsp.	15
Tangerine	1 large	100
Watermelon	1 cup	175

List 4. Bread Exchanges

Carbohydrate—15 Gm., Protein—2 Gm., Calories—68

	Measure	Gm.
Bread	1 slice	25
Biscuit, Roll	1 (2 in. diam.)	35
Muffin	1 (2 in. diam.)	35
Cornbread	1 (1 1/2 in. cube)	35
Flour	2 1/2 tbsp.	20
Cereal, cooked	1/2 cup	100
Cereal, dry (flake and puffed)	3/4 cup	20
Rice, Grits, cooked	1/2 cup	100
Spaghetti, Noodles, etc., cooked	1/2 cup	100
Crackers, graham (2 1/2 in. sq.)	2	20
Oyster	20 (1/2 cup)	20
Saltines (2 in. sq.)	5	20
Soda (2 1/2 in. sq.)	3	20
Round, thin (1 1/2 in. diam.)	6–8	20
Vegetables		
Beans and Peas, dried, cooked (lima, navy, split pea, cowpeas, etc)	1/2 cup	90
Baked Beans, no pork	1/4 cup	50
Corn	1/3 cup	80
Parsnips	2/3 cup	125
Potatoes, white, baked, boiled	1 (2 in. diam.)	100
Potatoes, white, mashed	1/2 cup	100
Potatoes, sweet, or Yams	1/4 cup	50
Sponge Cake, plain	1 (1 1/2 in. cube)	25
Ice Cream (omit 2 fat exchanges)	1/2 cup	70

List 5. Meat Exchanges

Protein—7 Gm., Fat—5 Gm., Calories—73

	Measure	Gm.
Meat and Poultry (med. fat) (beef, lamb, pork, liver, chicken, etc.)	1 oz.	30
Cold Cuts (4 1/2 in sq., 1/8 in. thick)	1 slice	45
Frankfurter	1 (8–9/lb.)	50
Fish: Cod, Mackerel, etc.	1 oz.	30
Salmon, Tuna, Crab	1/4 cup	30
Oysters, Shrimp, Clams	5 small	45
Sardines	3 medium	30
Cheese, cheddar, American	1 oz.	30
Cottage	1/4 cup	45
Egg	1	50
Peanut Butter*	2 tbsp.	30

* Limit use or adjust carbohydrate.

List 6. Fat Exchanges

Fat—5 Gm., Calories—45

	Measure	Gm.
Butter or Margarine	1 tsp.	5
Bacon, crisp	1 slice	10
Cream, light, 20%	2 tbsp.	30
Cream, heavy, 40%	1 tbsp.	15
Cream Cheese	1 tbsp.	15
French Dressing	1 tbsp.	15
Mayonnaise	1 tsp.	5
Oil or Cooking Fat	1 tsp.	5
Nuts	6 small	10
Olives	5 small	50
Avocado	1/8 (4 in. diam.)	25

TABLE III
Sample Diet Calculation
(Diet Prescription 80-80-185 (35–65–75–10))

Food	Amount	P	F	C
Milk Exchange, List 1	3 cups (standard)	24	30	36
Vegetable Exchange, List 2A	As desired	...	...	...
Vegetable Exchange, List 2B	2	4	...	14
Fruit Exchange, List 3	3	...	...	30
				80
Bread Exchange, List 4	7	14	...	105
		42		
Meat Exchange, List 5	5	35	25	...
			55	
Fat Exchange, List 6	5	...	25	...
TOTAL		77	80	185

CALCULATIONS:

Carbohydrate

185 Gm. carbohydrate in prescription

80 Gm. carbohydrate in diet from other than bread exchanges

105 ÷ 15 = 7 bread exchanges

Protein

80 Gm. protein in prescription

42 Gm. protein in diet from other than meat exchanges

38 ÷ 7 = 5 meat exchanges

Fat

80 Gm. fat in prescription

55 Gm. fat from other than fat exchanges

25 ÷ 5 = 5 fat exchanges

Food	Amount	C
BREAKFAST:		
Fruit Exchange	1	10
Egg (Meat Exchange)	1	..
Bread Exchange	1	15
Fat Exchange	2	..
Milk	1 cup	12
TOTAL		37
LUNCH:		
Meat Exchange	1	..
Vegetable Exchange, List 2A	As desired	..
Vegetable Exchange, List 2B	1	7
Fruit Exchange	1	10
Bread Exchange	3	45
Fat Exchange	2	
TOTAL		62
DINNER:		
Meat Exchange	3	..
Vegetable Exchange, List 2A	As desired	..
Vegetable Exchange, List 2B	1	7
Fruit Exchange	1	10
Bread Exchange	3	45
Fat Exchange	2	..
Milk	1 cup	12
TOTAL		74
BEDTIME:		
Milk	1 cup	12
TOTAL		12
GRAND TOTAL		185

TABLE IV

Menu Adaptation of Meal Plan

Meal plan		Menu	
BREAKFAST:			
Fruit Exchange	1	Orange juice	1/2 cup
Egg	1	Poached egg	1
Bread Exchange	1	Whole wheat toast	1 slice
Fat Exchange	2	Bacon	1 slice
		Butter	1 tsp.
Milk	1 cup	Milk	1 cup
LUNCHEON:			
Meat Exchange	1	American cheese	1 oz.
Vegetable Exchange			
List 2A	As desired	Lettuce for sandwich	
List 2B	1	Carrot sticks	1/2 cup
Fruit Exchange	1	Apple	1 small
Bread Exchange	3	Bread (for sandwich)	3 slices
Fat Exchange	2	Butter	2 tsp.
DINNER:			
Meat Exchange	3	Roast beef	3 oz.
Vegetable Exchange			
List 2B	1	Peas	1/2 cup
List 2A	As desired	Celery	As desired
Fruit Exchange	1	Peach	1 medium
Bread Exchange	3	Potato, mashed	1/2 cup
		Bread	2 slices
Fat Exchange	2	Butter	2 tsp.
Milk	1 cup	Milk	1 cup
BED TIME:			
Milk	1 cup	Milk	1 cup

usually expensive, often unpalatable, and tend to make the diabetic patient feel that his diet is different from that of others. This should not be the case. His diet is only a modification of the normal diet in carbohydrate content and therefore may include all but a few of the foods eaten by the average person. The only specially prepared foods that the diabetic patient need purchase are fruits canned or frozen without sugar.

SUMMARY

Every physician will find it of value to use the exchange system presented here for the calculation of the diets for his diabetic patients. This system provides a standard procedure to be followed by physicians and dietitians throughout the country, takes little time to calculate a diet for each individual patient, is easily taught to the patient, allows for a great variety of foods in the diet, and provides for adequate nutrition.—DORIS JOHNSON

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Nutritional Quotes

Dietary Safety Margins

"In interpreting the Recommended Dietary Allowances, it should be understood that they indicate levels of nutrient intake which appear to be desirable goals toward which to strive in planning diets and food supplies. The allowances are high enough 'to cover substantially all individual variations in the requirements of normal people' and to include a margin of safety above the critical and minimal level of each nutrient to 'permit additional benefits.' The nutritive intakes recommended are, in general, higher in average requirement and lower than the amount needed in pathologic states or in rehabilitation following depletion."

—G. A. Goldsmith. *Journal of the American Dietetic Association* 29: 109, 1953.

The Appetite and Protein

". . . the appetite responds to the state of metabolic inventory in such a way that the organism is motivated to eat when the inventory has been depleted and to reject food when items have accumulated. If we assume this, we can trace a sequence of cause and effect in the response to lower dietary protein. The first effect of lower dietary supply is a reduction in metabolic activity of proteins and derived metabolites. Because of the imbalance of rates, some of the other metabolites come to be in relative surplus. The appetite, therefore, and the inventory of the other metabolites is allowed to shrink until a new steady state is reached, a matter of several months in the case of protein restriction. Then the appetite returns to a balance with expenditure."

—V. P. Dole, L. K. Dahl, I. L. Schwartz, G. C. Cotzias, J. H. Thaysen, and C. Harris. *Journal of Clinical Investigation* 32: 185, 1953.

Milk and Skeletal Maturation

"The present findings clearly demonstrate that alteration in the pattern of skeletal maturation in children with nutritive failure may be reversed to a considerable degree by the supplementary feeding of reconstituted whole or nonfat milk solids. The removal of deficiencies of skeletal maturation in these children, regardless of age, appears to be primarily dependent upon the adequacy of the level of supplementation. Thus, children with chronic nutritive failure given supplements of cow's milk at a level equivalent in protein value to 3 qt. per week for a period of 4 months, showed little if any change in rate of bone maturation as contrasted with that of a comparable group not receiving the added milk. A fourfold increase in the quantity of milk supplements for a period of six months resulted in a readily detectable improvement in the overall rate of bone maturation in each of 19 children given the increased quantity of supplement."

—T. D. Spies, S. Dreizen, R. M. Snodgrasse, G. S. Parker, and C. Currie. *A. M. A. American Journal of Diseases of Children* 85: 9, 1953.

Child Nutrition and Child Psychology

"There is an established body of scientific research in the field of child nutrition which has told us what foods are important to the growing child and why. This knowledge has been applied widely and effectively in many ways to child feeding. . . . Yet the problem of poor nutrition has not been solved; feeding problems still abound. Anxious parents, nurses, physicians, child care workers, and nutritionists all testify to the prevalence of children with an assortment of feeding problems with far-flung implications, of grown-up children, 'adults,' with just as wide an assortment of distorted responses to eating, the most basic natural process. . . .

"We are beginning to recognize that feeding experiences have a powerful influence on a child's growing personality because from the beginning of life they occur as intimate relationships with other human beings who care for him, give to him, withhold from him, and come to expect certain kinds of behavior from him. The child's personality, directed from within by his own developmental forces, takes on its structure and form in the environment of these personal relationships. From the earliest beginnings of life, each offering of food to the infant brings from the person who feeds him some kind of answer to his hunger for love, which is a need as real in him as the hunger for food which first set him crying."

—M. V. Wallace. *Journal of the American Dietetic Association* 29: 449, 1953.

Obesity and Surgery

"It is obvious that a fat-laden abdominal wall is a severe handicap to a surgeon who is endeavouring to palpate an indefinite abdominal swelling, and, in the absence of clinical guidance, more reliance must be placed on laboratory and radiological examinations. In addition, fat buttocks relegate a digital examination of the rectum into an inadequate exploration of the anal canal, and a bimanual examination of a suspected pelvic swelling in a female is likely to be inconclusive. . . .

"In suitable cases, when delay of a few weeks is of little moment, it is wise to defer operative intervention in the obese until a medical colleague has prescribed and supervised a course of weight reduction with satisfactory results."

—McN. Love. *The Medical Press* 228: 482, 483, 1952.

Nutrition Briefs

RECENT ADVANCES IN EXPERIMENTAL NUTRITION

COMBINED INJECTIONS of epinephrine and thyroxine produced aortic intimal and medial sclerosis in rabbits. Massive doses of inositol inhibited this effect only slightly. Concomitant administration of ascorbic acid significantly lowered the incidence and lessened the severity of the lesions.

O. Davis and Y. T. Oester. *Proc. Soc. Exper. Biol. & Med.* 81: 284, 1952.

CORTISONE administered to rats on a purified diet containing casein and glucose showed inhibition of body growth, alopecia, and atrophy of the thymus. Vitamin B_{12} or aureomycin largely counteracted this effect. The combination of the two was more effective than either alone. Whole liver seemed more effective than either—which raises the question as to whether or not liver contains an unknown factor which counteracts this cortisone action. It appears that, experimentally, cortisone increases the requirement for vitamin B_{12} and other factors.

J. Meites. *Proc. Soc. Exper. Biol. & Med.* 81: 307, 1952.

VITAMIN B_{12a} (hydroxo-cobalamin), but not vitamin B_{12} (cyano-cobalamin) was capable of preventing toxicity and death in experimental cyanide poisoning. When potassium cyanide administration was followed by vitamin B_{12a}, some of the cyanide appeared in the urine as thiocyanate, but a greater proportion was detoxified by combination with vitamin B_{12a} to form vitamin B_{12}.

C. W. Mushett, K. L. Kelley, G. E. Boxer, and J. C. Rickards. *Proc. Soc. Exper. Biol. & Med.* 81: 234, 1952.

IN SPITE OF adequate amounts of choline or methionine, liver fat was above normal in rats on a 9 per cent protein (casein) diet. A normal liver fat picture was produced only upon the addition of 3 to 6 per cent casein or gelatin. A combination of 2 or more amino acids is needed, and must be present with methionine for a lipotropic effect.

C. A. Elvehjem. *Science* 116: 521, 1952.

THE RATE of healing of experimental wounds in animals is more rapid on a high protein diet. This is due to a greater intake and retention of sulfur, and both methionine and cystine have the same effect, per equivalent of sulfur. Some methionine, *per se*, is required for wound healing.

M. B. Williamson and H. J. Fromm. *Proc. Soc. Exper. Biol & Med.* 80: 623, 1952.

ADULT MALE rats were given small intraperitoneal injections of sodium pentobarbital. Amounts given did not reach levels which produce sedation. When doses were above 5 mg./Kg., food intake and nembutal were inversely related in an almost linear fashion.

P. S. Siegel and N. R. Ellis. *Am. J. Physiol.* 171: 22, 1952.

CURRENT OBSERVATIONS OF CLINICAL INTEREST

A PATIENT with scurvy demonstrated an abnormality in tyrosine metabolism which was promptly reversed by ascorbic acid. Citrovorum factor did not alter the abnormal tyrosine metabolism, nor did it change the abnormal capillary fragility.

G. J. Gabuzda, Jr. *Proc. Soc. Exper. Biol. & Med.* 81: 62, 1952.

INTRAVENOUS fructose is better than glucose for protein synthesis from infused amino acids, because it enters the cells as rapidly as the amino acids and can be metabolized for energy, leaving the other for protein synthesis. Glucose administered with amino acids is not immediately available, and hence the latter may have to be used for energy purposes.

R. Elman and T. E. Weichselbaum. *Science* 116: 521, 1952.

ON SELF-SELECTED mixed diets 3095 $\pm$ 1024 units of amylase were excreted in the urine by human subjects. These values were decreased by high carbohydrate, alkaline residue diets. High protein diets and fasting produced increases, while ketogenic and high purine diets were without effect. The authors suggest that this enzyme may have some function in the body other than in digestion.

B. W. Smith and J. H. Roe. *J. Applied Physiol.* 4: 666, 1952.

Nutrition News

News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the JOURNAL.

FAO FINDS WORLD FOOD PROBLEM ACUTE

In its report on "The State of Food and Agriculture: Review and Outlook, 1952" (Rome 1952), FAO presents statistics on world-wide production and consumption of food in the years 1951–52 which prove that postwar improvement has been followed by decline; in many countries consumption has fallen below prewar levels. India's caloric consumption has fallen from a prewar 1620 to below 1600 per day per person, and its daily consumption of animal protein is a mere 6 Gm. per day (compared to 61–62 Gm. per day in the United States.) Almost every Far Eastern country shows a similar decline below the prewar average. Downward trends (qualitative and/or quantitative) are apparent in Pakistan, Indonesia, Japan, etc. Greece, Italy, Austria, Germany, Denmark, and Ireland also show declines from prewar caloric and nutritional standards; and there has been no improvement in South America.

In the United States, on the other hand, the already high caloric intake has increased from 3170 to 3210, with a parallel increase in protein consumption. "Malnutrition" in the United States is therefore a matter of overnutrition, and not, as elsewhere, of undernutrition.

In summarizing the FAO statistics and the causes for the general worsening of the world's nutritional status, *Nutrition Reviews* (2: 112) points out the dangers inherent in this situation, one of which is the sharp contrast between the United States and the rest of the world. It rightly concludes:

"If greater knowledge leads to increased responsibility, then nutritionists have a special duty to inform the public on the nutritional situation of the world. Present conditions justify neither complacency nor relaxation of efforts in the fields of international trade or technical assistance."

RETIRING DIRECTOR-GENERAL OF WHO DELIVERS FAREWELL ADDRESS

Dr. Brock Chisholm, who will retire on July 21, 1953, after a five-year term as Director-General of the World Health Organization, delivered his farewell address to the closing session of the Sixth WHO Assembly on May 25, 1953, in Geneva. Dr. Chisholm reminded his listeners of the purposes and accomplishments of WHO, and of the many problems still to be solved. He stressed particularly the fact that health is only a part of the total problem, and one that cannot be disengaged from agricultural, social, and economic considerations.

"It is obvious," he said, "that even if health campaigns are carried out successfully in a community, they don't promote social progress merely by restoring health and working capacity of a number of its members. There has been no social progress if physically rehabilitated people merely swell the ranks of the unemployed, the dissatisfied and the hungry. . . . On the other hand neither investment capital nor improvement of agricultural methods will lead to increased productivity in underdeveloped countries unless adequate measures are taken to raise health standards of the people to the degree which will allow them to work efficiently both in agriculture and industry."

Obstacles to the success of WHO and other UN agencies are seen as political selfishness, narrow nationalism, and concentration on building strength and security through weapons of war rather than by universal improvement of social and economic conditions.

"Each one of us," said Dr. Chisholm, "must learn that the welfare of his own nation today is dependent on the welfare of all nations. Therefore we must acquire above all and help our children to acquire an equal degree of loyalty to all members of the world community

as a whole, irrespective of differences of race, religion, color or any other group characteristics."

In this type of cooperative endeavor, the role of WHO is paramount, since—as the preamble to its Constitution affirms: "The health of all peoples is fundamental to the attainment of peace and security."

Dr. Chisholm, a Canadian, will be succeeded by Dr. Marcolino Candau of Brazil, now Deputy Director of the Organization in the United States.

The Gourmet Challenges the Biochemist

"One wide field of biochemistry remains practically unexplored, and that is the scientific examination of the appetizing attributes of food. . . . The biochemist has unravelled a strange story of sequent explosions of organic phosphates and the culminating oxidation of carbohydrate, also the changing configuration of long chain carbon compounds. These are all fascinating investigations, but they throw no light whatsoever on skeletal muscle as it appears on the dining table. Why, for instance, should the psoas have a characteristic flavour absent from other and even adjacent muscles? . . . Veal is so different in its culinary appeal from the flesh of the adult ox or cow that an affinity is not recognizable; one might easily refuse to believe that the animal which yields veal could, if given a timely reprieve and allowed to grow, produce rump steak and ribs of beef. . . . Custom and law agree in denouncing the flesh of a female mammal which has just parturated as unfit for human consumption. Is there any biochemical basis for this belief? . . . Why should the fat of an adult river fish create difficulties in digestion and lead to unpleasant eructations whilst the fat of sea fish is almost or completely free from these disabilities? . . . We see therefore that many of the qualities which are responsible for flavour cannot at present be detected or assessed by any procedure other than human sensory faculties; but there must be a number, especially those which have been mentioned in connexion with foodstuffs derived from animals, with which the biochemist ought to get busy."
—"Biochemistry and the Kitchen." *Medical Journal of Australia* I (15): 515–516, 1953.

Nutrition as Analogy

"The vital fact about healthy human powers is that they develop by use in an environment which invites and facilitates such use; whilst they atrophy when disuse is their fate, either by reason of an inherent fault or an inhibiting environment. To be precise, it is not the poverty of the environment so much as the poverty or impossibility of response thereto, which results in atrophy and poor development. These principles are well illustrated in human nutrition. A thriving digestion and good food contribute to a robust appetite. It is a spiral of ascent and its end may be health. A poor digestion, on the other hand, and poor food endanger nutrition. It is a spiral of descent and the end will be disease."
—K. E. Barlow. *The Medical Press* 224: 402, 1953.

Antiquity of Disease

"Disease is more ancient than man. Evidence of disease has been found in dinosaurs and other forms of life which antedated man by millions of years. Then when man arrived on the scene, disease was waiting to meet him and constituted one of his earliest problems as soon as he became able to think at all. He observed that animals ate certain grasses and plants when they were ill and he proceeded to do the same. Then by trial and error he discovered that some plants were foods, others were drugs (such as purgatives), others poisons. His experiments dealt mainly with the vegetable world, and the majority of his remedies were derived from plants. All this was perfectly rational, and to this day we use some domestic medicines which our early ancestors discovered. Folk-medicine is probably the most ancient form of medicine."
—D. Guthrie. *Proceedings of the Royal Society of Medicine* 45: 92, 1952.

Reviews of Recent Books

Food in Health and Disease (fifth edition) by K. Mitchell, B.A., and M. C. Bernard, B.S., F. A. Davis Co., Philadelphia, 1953, pp. 688, $4.25.

The preface to the fifth edition of this book contains a statement which says: "this text is designed primarily for student nurses; the subject is approached from its relation to the nurse in her work in the hospital and in the community. As an aid to the young instructor an outline of classes is given." This is the reason why this book can be recommended highly for the purpose for which it was written. Only the necessary material which will be of value to the student nurse is included in the text. Preceding every chapter is a very useful outline of the material to be found in that chapter. This will save time for the instructor and the student. The charts used in the text have been reproduced from large wall charts which are familiar to, and are used by, many instructors.

The book is divided into 5 parts. The first 3 parts are divided into units. These units make the book useful in teaching. Food Exchange Lists used in the calculation of the diet for the diabetic are those recommended by the American Diabetes Association, the American Dietetic Association, and the U. S. Public Health Service. The Composition Table for Short Method of Dietary Analysis should be of value to students. The latest and most accurate figures for the sodium and potassium content of foods are given. The Diet History and Outline for Dietary Case Study found on pages 590–591 should prove a labor-saving device for the dietitian. The section on Community Nutrition reminds the student nurse of her responsibility to the community, as well as to herself and her patient. S.M.B.

Essentials of Infant Feeding for Physicians by Herman Frederic Meyer, M.D., Charles C Thomas, Springfield, 1952, pp. 252, $6.75.

This book contains a compilation of information and ideas on infant feeding which is based on long experience. Obviously, a great effort has been expended in assembling details concerning the composition and use of the great variety of commercial preparations. The author states in his preface that the purpose was to provide a concise manual which would be of use in the practical aspects of infant feeding. The book does not contain any original data and is not intended for those interested in the scientific basis of infant nutrition. The basic facts of nutrition are reviewed superficially to give some understanding of the rules which are provided for the composition of infant diets.

The book is devoted almost entirely to the feeding of normal infants. The feeding of sick infants is considerably more complicated and controversial, and a practising physician would be disappointed not to receive more help in this regard.

The author considers this book to be needed because of a supposed deficiency in the training of physicians in preparation for the feeding of normal infants and children. The information provided in most curricula on this subject is now very simple and adequate. If the student were led to believe that all the information in this book was necessary for successful feeding of infants, he would not only be considerably more confused than he may be at present, but the complexities encountered in infant feeding decried by the author would be perpetuated.

Great reliance is placed upon the "art" of infant feeding and this apparently is difficult to teach. It is possible that the complex state of affairs which exists concerning the multiplicity of foods and feeding arrangements proposed for infants is the result of a former era when there was intense preoccupation with minor variations in infant feeding and great faith in the "art" of infant feeding. As the author points out, infants are expected to thrive on the uniformly composed milk from the breast almost without exception; but he insists that when they are being fed artificially every infant presents a very individual problem. There are many reports of a large series of babies, representing a random sample of the population, thriving on an artificial formula of fixed composition without any need for individualization. This seems more in keeping with the laws of science which must govern the baby's physiology and digestion when artificially fed as surely as when the baby is fed at the breast.

The book contains many excellent statements of common sense practice in infant feeding and a thoroughly proper appreciation that breast feeding is preferable, though failure in this need not spell tragedy for the baby. It is a great relief from the dull prose of ordinary scientific writing to find the author has preserved a colorful and spirited style and the courage to express his opinions emphatically.

The book will be useful if one wishes to find out the details of a commercially prepared feeding upon which a baby has been placed. If more babies were fed on the simple programs utilizing whole cow's milk, the bulk of the book devoted to the analysis of commercial preparations would be unnecessary.

On the other hand, the convenient and carefully controlled preparation of complete infant formulae by commercial companies is becoming increasingly popular with the busy mother. She is less and less inclined to compound individually prescribed infant formulae on the back of the stove, just as she no longer finds it profitable to bake her own bread. That there should be intense competition between purveyors of the commercially prepared infant feedings would seem highly desirable from the point of view of obtaining quality products at economical prices. The only cure for extravagant claims in advertising is to turn out properly prepared doctors from the medical schools so that such advertising would not find a fertile soil.

In conclusion, this text is not recommended for use in medical schools and is not a fundamental manual of the scientific aspects of infant nutrition. For these purposes, standard texts and other excellent monographs would be preferable. C.D.M.

The Chemistry and Technology of Food and Food Products (three volumes, second edition) edited by Morris B. Jacobs, Interscience Publishers, Inc., New York, 1951, pp. 2580, $42.00.

This is the most complete and authentic publication in the English language on the chemistry and technology of food and food products. It was prepared by a group of 39 food technologists, chemists, chemical engineers, biochemists, bacteriologists, sanitary engineers, public health officers, food inspectors, and entomologists. In this second edition the editor and collaborators, who deserve to be congratulated for their excellent job, revised all the chapters of the first edition (1944) in the light of progress made in the intervening years. In addition new chapters have been added covering such topics as instruments in the food plant, essential oils, and the use of enzymes in food production. The new material has necessitated a third volume.

The three volumes are divided into six parts. In the first volume, the first part deals with the aspects of food chemistry, which are common to all foods; in part two, unit operations and processes applicable to most foods are described; and part three deals with maintenance and sanitary and quality control. The second volume, which comprises part four, concerns the descriptive aspects of particular food groups and includes some account of the history, statistics, definitions, standards, composition, and chemistry of these food products. In the third volume, the principal methods of preserving food are delineated in part five, and part six is concerned with production methods for the principal foods. Throughout the entire three volumes the role played by adequate nutrition in modern life is stressed.

There is, in certain respects, an overlapping of the subject matter, but as a rule, a food group is treated in two separate but closely integrated chapters. The editor maintains that in a collaborate effort it is always difficult to avoid duplication. Such duplication has been permitted when required to maintain the continuity of a chapter or to simplify an explanation.

Within the past six or seven decades great advances have been made in the application of scientific knowledge to the preparation, processing, preservation, and transportation of foods, so that it is possible to have foods in season throughout the year. The methods of production of our staple foods are much the same as in former years, despite vast improvement in the methods with consequent increase in yield, but it is in their distribution and packaging, and in the variety of processed foods produced and developed that great progress has been made recently. These changes are recorded in great detail in these books.

Food technology has made great achievements in all these years, but despite this progress, and despite the millions of people killed in the 1939–1949 period by war, famine, and pestilence, there is an ever-increasing world population. During the past decade there was an increase of 260,000,000 people in the world population. This increase is almost in accord with the theory of Malthus and the population is increasing much faster than available food supplies. Therefore, it must be the aim of the food technologist to increase the supply of food by fuller utilization of food from both land and sea sources, and by making palatable many wholesome foods not used at present because of lack of palatability.

In the chapter on proteins and amino acids the statement is made that, because arginine and histidine are not essential for the maintenance of nitrogen equilibrium in the adult man, it is questionable if these amino acids are needed in human diets. Amino acids are essential for many vital physiological functions in addition to their requirements for nitrogen equilibrium i.e., for hematopoiesis, for synthesis of hormones and enzymes, for respiration, for spermatogenesis, for maintenance of the osmotic pressure of the blood, and for antibody formation. For instance, Holt and Albanese* found diminished spermatogenesis in human subjects on an arginine-deficient diet. Furthermore glycine and glutamic acid are generally considered as non-essential amino acids for growth of mammals, but both of these, being components of glutathione, are essential for vital oxidation-reduction reactions in the animal body. One must, therefore, be very cautious in pronouncing certain amino acids as not being needed for human welfare until convincing clinical evidence is available that they can be synthesized for all vital physiological processes, including reproduction and lactation.

The term *vitagen* used in chapter VII should be

* Holt, E. L., Jr., and Albanese, A.: Observations on amino acid deficiencies in man. *Trans A. Am. Physicians* 58: 143, 1944.

made clear, since it is not often used in the nutritional and medical literature. The author refers this term to the essential fatty acids, essential amino acids, choline and related compounds, the essential transferable methyl group, and the essential organic sulfur-containing compounds. Vitagens are differentiated from vitamins according to the function of these compounds in the organism. The vitagens are essential not only as transformers of energy or regulators of the metabolism of structural units, but also as suppliers of energy or as structural units. On the other hand, the vitamins act as catalysts in vital metabolic reactions, and not as structural units of the animal body.

In chapter XXIV there is considerable valuable information on the thiamine, riboflavin, and niacin content of cereal grains but data are lacking on the distribution of other B vitamins, such as pyridoxine, pantothenic acid, choline, and folic acid, which are now available in the nutrition literature. B. SURE

Blood Cells and Plasma Proteins: Their State in Nature, *Memoirs of the University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University, Number II* edited by James L. Tullis, Academic Press, Inc., New York, 1953, pp. 436, $8.50.

This is a scholarly book dealing with blood cells and plasma proteins. It clearly and thoroughly reviews our present information about blood coagulation, immune processes, origin, properties, function, and preservation of red and white blood cells, and the enzymes of plasma. There are many references and a convenient author and subject index. There are chapters by twenty-nine authorities in the field of hematology and physical chemistry.

Although some chapters will be of interest primarily to investigators in the particular field, some may be read with profit by all physicians.

In this "coordinated picture of the current state of knowledge about blood and its component parts" the interested reader will find the best summary of current data on the subject. S.O.W.

Physiologic and Therapeutic Effects of Corticotropin (ACTH) and Cortisone by D. J. Ingle and B. L. Baker, *American Lectures in Metabolism* (edited by P. György, L. Leiter, and S. O. Waife), Charles C Thomas, Springfield, 1953, pp. 139, $5.50.

This little book is the most complete current summary of the clinical and experimental aspects of ACTH and cortisone that has appeared. With 324 references the book covers all the aspects of the effects of these hormones that would be of interest to clinicians or investigators An interesting feature is the inclusion of photographs of eleven outstanding students of this phase of endocrinology

As an authoritative, readable survey of the field, the book can be highly recommended. A.E.S.

Diseases of Metabolism (third edition) edited by G. G. Duncan, W. B. Saunders Co., Philadelphia, 1952, pp. 1179, $15.00.

The third edition of this well-known standard work continues to be the most thorough on the subject available today. Several chapters have been rewritten and enlarged. The twenty contributors are all prominent in their field and there are many references to the current literature. Vitamins are covered by Spies and Butt, obesity by Evans, undernutrition by Keys, diabetes by Duncan, to mention but a few sections.

The boundaries of "metabolism" are diffuse, as are the boundaries of "nutrition." Thus there is a 78-page chapter on diseases of the thyroid, presumably because the thyroid regulates metabolic activity. By the same token, the pituitary and adrenal glands could have been included. Similarly, there are chapters on diseases of the kidney and diabetes insipidus. One might therefore expect a discussion on liver diseases. These comments in no way are meant as criticism, since each section is very well done. The interrelations between metabolism, nutrition, and endocrinology are apparent from the contents of books on these subjects.

Although written with emphasis on clinical application, there is also a more than adequate discussion of basic physiology and biochemistry.

The book can be highly recommended to all physicians caring for patients with metabolic disturbances. S.O.W.

Man's Foods by L. B. Jensen, Ph.D., The Garrard Press, Champaign, Ill., 1953, pp. 278, $4.50.

Athenaeus observed that "every investigation which is guided by principles of Nature fixes its ultimate aim entirely on the gratification of the stomach." One may take exception to the word "ultimate," but it can scarcely be denied that the gratification of the stomach must precede all other aims. The whole history of man and man's societies can only be understood in terms of his food—how he obtained it, how he used it. The very names used by anthropologists to describe the various types of human societies are indicative of the way food defines a culture: "hunting," "food-gathering," "agricultural." The gradual perfecting of tools by the primitive hunter was the first stage in the development of man's mechanical genius. The anonymous women who experimented with baking and brewing techniques were the world's first chemists. And the first people to think of domesticating animals to insure their food supply laid the foundations for the more stable societies of the future—societies in which the arts of leisure became possible.

The search for food not only led to basic practical discoveries; it involved the whole of man's life, spiritual as well as physical. The magnificent art of the cave man grew out of his concern with hunting

magic, and primitive man's relationship to his gods was largely that of a petitioner for his "daily bread"—in the next life as in this.

It is not surprising, then, that a book should have been written which treats man's history as the history of man's foods. In Dr. Jensen's volume, the nutritional background of human life—tacitly accepted by all the disciplines concerned with the study of man—is placed in the foreground, where it quite properly belongs.

Much of the nutritional record is, of course, dim, and the evidence is fragmentary. Mammoth meat, deep-frozen for 10,000 to 15,000 years, has been consumed with impunity by contemporary diners; well-preserved Neolithic grains have been analyzed and classified; bone counts have indicated the proportion of each type of animal in the diet of various prehistoric peoples; and ancient garbage heaps have been instructive. But often the prehistoric diet has had to be inferred from what is known of the flora and fauna of the era, and from unsatisfactory analogies with the diet of contemporary primitives. Attempts to correlate past diet with anthropometric or other evidence of health and longevity are still more difficult. In Paleolithic times the diet seems to have consisted of nutritionally excellent items (including human flesh), but the food supply was uncertain and the hunter might alternately gorge and starve. In more advanced periods, the diet might be steadier and better, but village and urban life increased the hazard of infection, thus cancelling the possible effects of good nutrition on longevity. It is therefore hard to disentangle from the total picture of an era and environment any clear correlation between type of diet consumed and type of human being produced. Certain facts are, at least, suggestive: that the Classic Greeks ate all of the "basic seven" foods, abhorred overeating, and lived longer lives than any population till modern times; that certain Mesolithic groups subsisting largely on shellfish (with its thiamine-destructive enzyme) were "puny" and culturally stagnant, compared to earlier meat-eaters; that the Jews, with their strict dietary laws, managed to outlast their less hygienic contemporaries; and that democracy has never appeared where the food supply was inadequate.

One thing emerges clearly from the record. When we consider how various has been the fare of mankind since first he appeared, we are forced to the chastened recognition of the fact that the modern western diet is as much the result of "taboos" as is that of any primitive group—since there is no basis in nutrition or health for the rejection of horse meat, dogs, grubs, caterpillars, locusts, or many other foods consumed without scruple by other peoples, past or present.

When an author is dealing with so many different specialties, he is sure to excite the objections of one or another specialist. The anthropologist may frown at the statement that the Maya and the Incas were the only "civilized" groups in pre-Columbian America. (How about the Aztecs? We have seen, quite recently, that "civilization" does not preclude cruelty.) Nor would all nutritionists subscribe to the categorical statement that "The actual cholesterol content of man's diet is of no importance in developing arteriosclerosis." One also dislikes to criticize an author for what is probably the result of over-enthusiasm for his background subjects, but there are so many "interesting asides" that the main topic gets lost occasionally and one finds oneself digesting extraneous archeological or philosophical matter instead of "food." Sometimes, too, the leaps backward and forward in time are a bit disconcerting; a recent experiment with a rat population is apt to intrude suddenly on a consideration of a prehistoric human population. More careful organization of the material and elimination of repetition would have made the reader's task a little easier; but with patience he can follow the nutritional thread through the volume's somewhat labyrinthine course.

The subject index is a helpful guide, and there are 21 pages of references, where anthropologists, archeologists, and explorers consort with biochemists and nutritionists.

The interested reader—and no reader could fail to be interested—will certainly collect a lot of fascinating facts and acquire a heightened appreciation of the role of food in shaping human life. Food has always been man's basic problem and it is still his major one. The millennial war against hunger is not yet won, and our future history will depend to a great extent on how—and by whom—the gratification of the world's stomach is assured. C.-J.H.

Books received for review by the *Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Current Therapy 1953, edited by H. F. Conn, W. B. Saunders Co., Philadelphia, 1953, pp. 835, $11.00.

The Low Sodium Cook Book by A. S. Payne and D. Callahan, Little, Brown & Co., Boston, 1953, pp. 477, $4.00

Food Science, edited by E. C. Bate-Smith and T. N. Norris, Cambridge University Press, New York, 1952, pp. 319, $8.00.

General Biochemistry by J. S. Fruton and S. Simmonds, John Wiley & Sons, Inc., New York, 1953, pp. 940, $10.00.

Refrigeration in America by O. E. Anderson, Jr. Princeton University Press, 1953, pp. 344, $6.00.

Abstracts of Current Literature

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AMINO ACIDS

The wide clinical use of intravenous amino acid preparations for purposes of maintaining or supplementing nitrogen intake may represent a waste of the material and a needless expense to the patient in many instances where attention is not given to the rate of administration. It is interesting to note in the following paper that up to 70 per cent of the infused amino acids were accounted for as urinary urea.

Studies on Metabolism and Disposal of Amino Acid Mixtures Given Intravenously. W. M. Mulholland, E. M. Bridge, and H. W. Fox. *Pediatrics* 10: 381, 1952.

This paper provides a large body of valuable data concerning the fate of intravenously infused amino acid mixtures. Studies were performed in rabbits and consisted in a constant intravenous infusion of 1 Gm. of casein hydrolysate per Kg. per hour over a period of 8 hours. It was found that approximately 5 per cent of the infused material appeared in the urine directly as amino nitrogen. Another 1 or 2 per cent remained in the blood stream but quickly disappeared when the injection was discontinued. Sixty to 70 per cent of the infused material appeared in the urine as urea, presumably as a result of deamination, and another 10 to 20 per cent in the form of other nitrogenous metabolites.

From the results in this study, the author suggested that amino acids from an infusion remain available for tissue synthesis for only a few hours at most. It is, therefore, suggested that a large infusion of amino acids given rapidly 2 or 3 times a day would not be as valuable as a smaller injection given continuously so as to permit maximum utilization. No harmful effects of the injections were noted and particular attention was paid to any effects on renal function, which was unimpaired.—C. D. MAY

However, excessive quantities of amino acids may have deleterious effects.

Effect of Excess Essential Amino Acids on Growth of the White Rat. W. C. Russell, M. W. Taylor, and J. M. Hogan. *Arch. Biochem.* 39: 249, 1952.

The addition of a quantity of methionine which is 200 per cent in excess of the amount suggested as the requirement by Rose and Womack caused a reduction in growth rate of about one-half. Feeding the same level of excess of the remaining nine essential amino acids gave results which indicated that lysine excess caused a marked depression of growth and valine a somewhat smaller depression.

It is concluded that the growth-depressant effect of lysine and methionine is a property of these compounds and is not due to amino acid imbalance.—M. K. HORWITT

Impairment of absorption in the edematous gastrointestinal mucosa of hypoproteinemic patients was observed and has important clinical implications.

Jejunal Absorption of an Amino Acid Mixture in Normal and in Hypoproteinemic Subjects. J. O. Hardy and J. Schultz. *J. Applied Physiol.* 4: 789, 1952.

Normal subjects absorbed an average of 36.8 per cent and hypoproteinemic patients absorbed an average of 27.9 per cent of nitrogen from casein hydrolysate perfused through a closed loop of jejunum. This difference is statistically significant. All but one of the hypoproteinemic patients were edematous. In the nonedematous patient N absorption was compar-

able to that of the controls. The suggestion is made that edema of the intestinal mucosa may have impeded absorption, a hypothesis which is supported by other findings (Elman) that casein hydrolysate was poorly utilized by hypoproteinemic patients who had edema. However, in an earlier study (Althausen), it was found that patients with heart failure absorbed galactose normally.—M. J. OPPENHEIMER

In order to establish nitrogen equilibrium in individuals receiving protein hydrolysates, it has been found necessary to supplement these with certain of the essential amino acids. The addition of these essential amino acids results in a product of higher nutritional value which is capable of maintaining nitrogen equilibrium in quantities considerably lower than those required for the unsupplemented hydrolysates.

Nitrogen Requirement of Normal Men on a Diet of Protein Hydrolysate Enriched with the Limiting Essential Amino Acids. W. S. Hoffman and G. C. McNeil. *J. Nutrition* 44: 123, 1951.

It is now generally recognized that it is possible to obtain positive nitrogen balance in human subjects on intravenously injected protein hydrolysates as the only source of nitrogen when supplemented with the limiting amino acids in pure form. Even when hydrolysates are prepared from good proteins, such as casein, the relative amounts of essential amino acids in the mixture are different from those of an ideal mixture of amino acids based on the true minimum requirements of the amino acids. However, if such hydrolysates are supplemented with the limiting amino acids in pure form, the requirement for nitrogen equilibrium of the supplemented product is less than that of the original product, and its nutritional value is considerably higher.

Nitrogen balance experiments were conducted on 7 normal male human subjects to determine the nitrogen requirements for equilibrium when the only significant source of nitrogen was a lyophilized casein hydrolysate given orally. Then in the same subjects the nitrogen requirement for equilibrium was determined for the same hydrolysate supplemented with *dl*-tryptophane, *l*-phenylalanine, and *dl*-methionine. The corrected mean nitrogen requirement for equilibrium with the unsupplemented product was 52.2 mg. per Kg. per day, and for the supplemented hydrolysate the mean nitrogen requirement for equilibrium was 38.5 mg. per Kg. per day.

Nitrogen equilibrium was reached with the unsupplemented product when tryptophane and methionine were present in the diet in quantities of the order of the minimum amounts found to be required by W. C. Rose. Therefore, these amino acids were the limiting factors determining the amount of nitrogen in the product required for equilibrium. However, nitrogen equilibrium was reached with the supplemented product when all the essential amino acids were present in twice as great a quantity as Rose had found necessary to meet the minimum requirement; consequently, the limiting factor in the supplemented product appeared to be the total quantity of nitrogen present. This conclusion was corroborated when the addition of 15 Gm. glycine changed from negative to positive the balance produced by a diet of 30 mg. per Kg. per day of the supplemented product.—B. SURE

The urinary excretion of amino acids is not necessarily dependent on the biological value of dietary protein. The patterns of amino acid excretion show no differences to exist between the sexes, if the metabolic body size is employed as the basis for comparison.

Urinary Excretion of Essential Amino Acids by Human Subjects Fed Diets Containing Protein of Different Biological Value. E. S. Nasset and R. H. Tully, III. *J. Nutrition* 44: 477, 1951.

Five men and 5 women students 21 to 30 years of age participated in the first 2 dietary periods. In the remaining 4 periods one of the women was absent. The dieting periods varied from 4 to 7 days. The urines were collected on the last 2 days, diluted to a volume of 2000 ml. and stored in the cold under toluene until analyzed. Aliquots from each day were combined for the amino acid determinations in the urine for each male subject. Because of lack of time and facilities, all urines from the females were pooled and analyzed as a single sample.

In most experiments, the males excreted larger amounts of essential amino acids than the females, but on the basis of body weight or metabolic body size no sex difference was evident.

With the possible exception of histidine and threonine, the pattern of amino acid excretion was unchanged and the absolute amounts were very little changed by adding various proteins to a protein-free diet. No correlation was found between the biological value of ingested protein and the total amount of essential amino acids excreted in the urine.—B. SURE

It is interesting to note that the administration of certain amino acids is associated with an increase in the output of bile acids. The possible effect of this mechanism on lipid metabolism should be investigated.

Dietary Factors Influencing Output of Bile Acids: Role of Amino Acids. D. F. Magee, K. S. Kim, and A. C. Ivy. *Am. J. Physiol.* 169: 317, 1952.

The output of cholate is increased approximately 25 per cent by an addition of 42.6 Gm. of the ten essential amino acids and glycine. This was true when these essential acids were added in the same proportions as in casein. It was shown that lysine, glycine, and the *d*-amino acids are not involved in this effect. Methionine, threonine, and valine increase the cholepoietic response due to ketogenic amino acids. Vitamin B_{12} increases cholate output tran-

siently. Cortisone acetate or testosterone propionate do not do so.—M. J. OPPENHEIMER

CALCIUM

The dietary requirements for calcium have been studied for many years without any unanimity of opinion having been reached. The effect of phosphorus intake, phytic acid, and oxalate on calcium absorption may be a factor in producing some of the varying results recorded. In the following study, the influence of phosphorus upon calcium absorption has been carefully analyzed.

The Effects of Levels of Intake on Calcium and Phosphorus Metabolism in College Women. J. M. Leichseuring, L. M. Norris, and S. A. Lamison. *J. Nutrition* 45: 407, 1951.

The subjects for this study were healthy college women ranging in age from 20 to 30 years. Eight were students at the Ohio State University and 9 at the University of Minnesota. Each student was given a physical examination by the University Student Health Service to insure that only healthy individuals were included. The basal diet, which contained 2140 calories and 50 Gm. protein, was supplemented with 300 mg. of calcium and 900 mg. of phosphorus daily. These levels were chosen as representing the lowest levels compatible with the serving of appetizing meals. Sugar was allowed *ad libitum* but a record was kept of the amount consumed by each subject. Distilled water was used for food preparation and drinking purpose and pure sodium chloride as seasoning. The subjects were requested to use the pure salt as a dentifrice, since many toothpastes contain appreciable amounts of calcium. These 17 subjects were maintained on the basal ration for 8 weeks. A second group of 6 subjects were maintained on the basal diet for 4 weeks, followed immediately by a 4-week period when the basal ration was supplemented by 1200 mg. calcium, making the total calcium intake 1500 mg. daily. A third group of 6 subjects following the 4-week period received supplements of calcium and phosphorus making the total intake of 1500 mg. calcium and 1400 mg. phosphorus.

One week was shown statistically to be an adequate period for adjustment to the calcium and phosphorus levels in the basal diet. Negative calcium balances were observed on the basal ration, whereas more positive than negative phosphorus balances were noted.

Increasing the calcium intake from 300 mg. to 1500 mg. daily without altering the phosphorus intake resulted in a noteworthy increase in calcium retention. Urinary calcium excretion also increased significantly. Phosphorus retention was unchanged, but there was a decrease in urinary excretion of this element. When supplements of both calcium and phosphorus were added to the basal diet, calcium retention was somewhat greater than in the unsupplemented basal diet but was very much less than when the basal diet was supplemented with calcium alone. Phosphorus retention, however, was not influenced by these changes in calcium and phosphorus intake. —B. SURE

Remarkably low dietary calcium intakes, sustained over long periods of time, have not produced manifestations of calcium deficiency in adult males.

A Study of the Minimum Calcium Requirement of Adult Men. D. M. Hegsted, I. Moscoso, and C. Collazos CH. *J. Nutrition* 46: 181, 1952.

The 10 volunteers who served as subjects were inmates of the Central Penitentiary of Lima, Peru. They ranged from 30 to 56 years of age. A medical history of each revealed no chronic or recent illnesses. No serious abnormalities or symptoms of nutritional deficiencies were found on physical examination. The subjects had been imprisoned for periods varying from 2 to 20 years. During this time they had received the prison diet plus occasional food gifts brought in by their families. It consisted principally of rice, bread, potatoes, spaghetti and beans. Meat was served once a day in limited amounts. Fresh vegetables were served frequently. Fruits other than bananas were rare. The only milk received was in one serving of chocolate once a week in place of the usual black coffee or tea. This diet was deficient in calcium, riboflavin, animal protein, and ascorbic acid when compared to the National Research Council's recommended dietary allowances. (Food and Nutrition Board, 1948). Yet, this diet must have been adequate to maintain the men in remarkable health over long periods of time.

The estimated calcium requirement to maintain balance in these men was between 100 and 200 mg. per day. A review of the literature reveals no solid evidence that calcium deficiency occurs in adult males. The minimum calcium requirement of adult males is probably so low that deficiency is unlikely in most natural diets. The authors conclude that when calcium supplies are limited, little effort should be made to increase the consumption of calcium by adult men. Available calcium, they maintain, should be reserved for children and women in childbearing age.—B. SURE

Although the above paper questions the need for calcium supplements in the adult, the following study is directed toward the finding of suitable forms of calcium which may be utilized to increase the intake of this mineral. Apparently all of the salts tested were absorbed to an extent corresponding with that of calcium from food sources.

The Utilization of Calcium from Lactate, Gluconate, Sulfate and Carbonate Salts by Young College Women. M. B. Patton and T. S. Sutton. *J. Nutrition* 48: 443, 1952.

Calcium salts are often used as a source of calcium for comparison in experiments designed to study

utilization of calcium from different foods. It is also a common practice for the physician to recommend the use of tablets of calcium salts to supplement that from food sources at times when large amounts are needed, such as during pregnancy and lactation. It has been found in studies of the dietary habits of older persons that many of them consume diets inadequate in calcium, and if they have not been accustomed to drinking milk, it is difficult to get them to increase their calcium intake by this means. Calcium salts have been used in such cases. In order to improve diets of the general population, particularly under emergencies such as war conditions, calcium salts have been used in the enrichment of breadstuffs and meat products. Under still other conditions, due to unequal distribution or inadequacies of food supplies, calcium salts have been recommended as a means of increasing calcium intakes. Hence it seemed desirable to compare the utilization of calcium from some of the salts that are used as supplements.

A study was made of the utilization of calcium by 9 college women from 4 salts (gluconate, lactate, carbonate, and sulfate) given in amounts equivalent to 400 mg. of calcium daily. The basal diet contained an average of 347 mg. of calcium daily and calculation of other nutrients showed that the diet was adequate. Statistical analysis of the balance data was made by the method of least squares. No significant differences in the utilization of calcium from these salts were found, the calcium from the less soluble salts being utilized as well as that from the more soluble ones. The order in which the salts were taken was shown to be a significant factor in the utilization. In the majority of the cases, the salt taken first was utilized to the largest percentage, regardless of which salt it was. The average percentage utilization from all salts for all subjects was approximately 18 per cent, a value within the range of those reported in the literature for utilization of calcium from food sources.

Young women having normal basal metabolic rates showed somewhat greater percentage utilization of calcium from salts than those whose rate was below the predicted normal.

The serum calcium levels were normal, 9 to 11 mg. per 100 ml, during the 8 weeks of the study and were practically the same for the periods when the 4 salts supplemented the basal diet.—B. Sure

Calcium Retained by Young Women before and after Adding Spinach to the Diet. F. A. Johnston, T. J. McMillan, and G. D. Falconer. *J. Am. Dietet. A.* 28: 933, 1952.

Six women, 20 to 31 years of age, during 12 weeks on a controlled diet consumed a basal diet supplying 820 mg. calcium daily for 4 weeks, and the basal supplemented with 120 Gm. spinach for the last 8 weeks. The spinach supplied 0.60 Gm. oxalic acid and 155–160 mg. calcium. In the basal period, the mean calcium loss for all subjects was 26 mg.; in the two spinach periods (4 weeks each) the losses were 30 and 51 mg. respectively. A "t" test for the differences between the retention on the basal diet and on the spinach diet showed that the increased loss in the last 2 periods was not significant.

The authors state: "the addition of spinach to the diet did not alter significantly the calcium balance. Consequently, the conclusion was drawn that an amount of calcium equivalent to that in the spinach failed to be retained."

Since the data show considerable weekly variation in fecal calcium for each subject, the reviewer believes addition of this small amount of calcium even in the form of milk, generally thought to be well utilized, might not have shown a significant advantage in calcium balance in the presence of the large fecal variation recorded.—J. M. Smith

The dynamics of calcium metabolism have been recently elucidated by workers employing radiocalcium. The disposition of ingested or injected calcium can be carefully traced by the use of this new tool.

Dynamics of Calcium Metabolism: Time Distribution of Intravenously Administered Radiocalcium. R. O. Thomas, T. A. Litovitz, M. I. Rubin, and C. F. Geschickter. *Am. J. Physiol.* 169: 568, 1952.

The authors were able to demonstrate that bone activity may be evaluated by a mathematical analysis of the disappearance of injected radiocalcium from blood when combined with excretion data. Four exponential terms are necessary to represent the mathematical analysis of blood disappearance curves. The exchange between plasma and extravascular compartments is indicated by the first two terms. There was no difference between young and adult rabbits. In young animals bone uptake was faster. It was possible to show a correlation between the third term and the uptake of calcium by bones. The authors are of the opinion that this term is a measure of bone activity. It would be a very useful fact if the blood disappearance curves for calcium could indicate bone exchange and thus be a measure of the physiological activity of bone. The fourth term appears to depend on urinary and fecal excretion during the first few hours of the postinjection period. There is an inverse relation between this fourth factor and bone uptake.—M. J. Oppenheimer

EXOTIC FOODS AND DIETARY PATTERNS

The following papers deal with some of the edible plant forms found in the diets of various ethnic groups and with the dietary patterns of several primitive populations, whose diets are assessed in terms of nutritional adequacy. Food lore, taboos, and methods of preparation reflect the physical and cultural milieu. Available resources are usually wisely utilized. The

fact that many primitive peoples were free of certain diseases from which "civilized man" suffers until the introduction of his foods into their diets is suggestive.

Seaweeds and their Value in Foodstuffs.. W. A. P. Black. *Proc. Brit. Nutrition Soc.* 12: 32, 1953.

Seaweeds belong to a group of plants known as the algae which are the lowest and simplest of all the plants in the plant kingdom. They are divided into four groups: the brown, red, green, and blue-green algae. The brown and red algae are the most important, partly because of the nature of the materials they contain and partly because they occur in sufficient quantity to possess an economic value.

In the East, seaweeds form an important constituent of food supplies. In Japan seaweed is used to a far greater extent than in any other country and is said to provide about 25 per cent of the daily diet. The brown seaweeds are incorporated in the flour and are used in almost every household as noodles, toasted and served with rice or in soup. Two species, *L. japonica* and *L. angustata*, because of their high content of mannitol and glutamic acid, are used for sweetening and flavoring.

In the West, seaweeds have never really been accepted in the diet and have only been eaten in times of scarcity and where the standard of living has been low. In Scotland, Porphyra (red algae) is still eaten. Grilled on toast, it looks like spinach and tastes like oysters and is made into laverbread, the national dish of South Wales.

In common with land plants, seaweeds contain carbohydrates, fats, proteins, vitamins, and a high percentage of minerals. The protein of algae, as in most other plants, is less assimilable than proteins of animal origin. The brown algae contain from less than 1 to 9 per cent fat. The following fats have been identified in the algae used in Japan: capric, caproic, caprylic, linolenic, oleic, myristic, palmitic, and stearic. The mineral content varies from 10 to as high as 50 per cent. In a balanced diet, they may prove to be an excellent mineral supplement as they contain all the mineral elements that have so far been shown to be essential in the physiological processes of man. Seaweeds are a very important source of vitamins and appear to be similar to green vegetables in their vitamin content.

For centuries the red algae have been used in small quantities in the food industries. *Porphyra laciniata* used to be eaten as a vegetable with vinegar and pepper under the name of "laver" in Wales, "sloke" in Ireland, and "slack" in Scotland.

The most red algal polysaccharide is agar which was originally the Malay name for certain East Indian red algae, but it is now almost exclusively used for the dried gelatinous extract. Agar has been and is still used as a food article in a great variety of ways in China and Japan. In Japan agar is served in such foods as agar-rice and agar cakes. Because of its low digestibility, agar is often used in certain bakery products in Scotland as a source of roughage.

Seaweeds, despite the many contradictions in the literature, do appear to have some nutritive value, while at the same time providing vitamins and the mineral elements essential for health, but as they are unpalatable and unacceptable to the people in the Western hemisphere, it appears they will have greater value as feed to animals destined for human consumption.—B. Sure

Mushrooms and Toadstools. J. Rambsbottom. *Proc. Brit. Nutrition Soc.* 12: 39, 1953.

Amanita muscaria is the one toadstool which most people can recognize and which is generally regarded as the most poisonous because of its bright red cap. It is not, however, deadly. Muscarine was first isolated from it but usually occurs in small amounts. Several species of *Clitocybe* and *Inocybe* contain muscarine in amounts sufficient to cause intensive sweating. The characteristic symptoms of cerebral excitement are due to mycetoatropine. *A. pantherina* has the same poisons and produces similar symptoms, though it is reputed to be somewhat more dangerous.

In England, there is no need to look for fungi for nutriment, but it is not always so elsewhere. In New Guinea, there is a small cave-inhabiting tribe whose plant foods consist largely of fungi and palm sprouts. In countries with severe winters where it is impossible for the peasants to obtain vegetables, fungi are collected in the autumn and dried, or pickled in brine. In religious sects where the eating of meats is forbidden at certain times, great use is made of fungi. This is particularly so during the three great fasts of the Russian Greek Orthodox Church.

In the two world wars, fungi were much sought after by starving peoples on the Continent. Refugees to England were often amazed at the British disregard of fungi they knew as delicious food. During the first world war, fungi were found most valuable in the French Cameroons, and the German forces constantly on the run in the East Africa Campaign were often compelled to exist almost entirely on them.

There have been many chemical analyses of different species of mushrooms and toadstools. Great variations in chemical composition have been found between various species and comparison is sometimes difficult because many of the analyses are of dried amounts of sodium, calcium, magnesium, iron, phosphoric acid (as lecithin) with small and varying material. The minerals are chiefly potassium and manganese, aluminum, silicon, sulfur, and chlorine in the skin of the cap. Of the nitrogenous material 45.4–84.0 per cent (average 66.8 per cent) is assimilable, as is about 95 per cent of the carbohydrate. For maintenance of nitrogen equilibrium in a normal person weighing 70 Kg., from 43 to 62 Gm. of total nitrogenous substance, corresponding to 100–200 Gm. of dried mushroom, were necessary, if mushrooms

were used as the sole source of protein in the diet.

Toadstools, in general, cannot be considered as a valuable source of vitamins. The only good source of thiamine was *Lacturius deliciosus* with 37 I.U. per 100 Gm. They generally seem to be poor in ascorbic acid. Fungi as a whole are rich in ergosterol.—B. SURE

The Indigenous Foods of Mexico and Central America. F. Aylward. *Proc. Brit. Nutrition Soc.* 12: 48, 1953.

This is a review of the work carried out by Professor Robert S. Harris and his colleagues of the Massachusetts Institute of Technology. The results obtained led to a new outlook on nutritional problems in Mexico and Central America.

The staple crop of Central America and Mexico is maize, from which comes the daily bread of the Indians—the *tortilla*—a flat cake of unleavened corn meal. Records are available of the recommended daily allowances in the Aztec tribes: a child (after weaning at 3 years of age) is given half a *tortilla* a day; from 4 to 5 years, one *tortilla*; from 6 to 12 years, one and a half *tortillas*, and at 13 two *tortillas*. Apart from maize, many other plants are employed by the Indian to give flour and bread, in particular a variety of nuts, such as chestnut, hazel-nut, acorns, and also, in some areas, sunflower seeds, which are also used as a source of edible oil. The root crop manioc or cassava is now the great staple food of Brazil but is common also in Central America and is widely used by the Indians where the climate is too hot for corn. The cassava, which gives us tapioca, is used in many ways. Cassava bread is made by grating the root and squeezing into a type of basket press. The solid is then formed into cakes and baked. The plant is also boiled and eaten as a vegetable.

Our cocoa and chocolate are prepared from the cacao plant grown in Central America. It was the favorite beverage of the Aztec emperors and one Spanish explorer reported that "it was so nutritious that a single cup was enough to sustain a soldier through the longest day's march."

The traditional alcoholic drink of the Mexicans is *pulque*, which is prepared by the fermentation of the juice of the *maguey*, a cactus of the Agan family. Its roots are eaten as a vegetable and its leaves provide a thatch for houses and are used in preparation of a paste and type of paper.

The collection of samples of edible plants of Central America extended from 1946 to 1949, during which time 924 samples, representing more than 200 kinds of foods were analyzed for their content of moisture, nitrogen, fiber, fat, ash, calcium, phosphorus, iron, carotenoids, thiamine, riboflavin, niacin, and ascorbic acid. The following are some of the comments on the plants: *Tampala* one of the pigweeds, is used occasionally as a canned vegetable. *Bledo extranjero* is used like spinach or mixed with onion and boiled, then fried in batter. *Chipilin* is used as a green vegetable, in soups and stews or cooked with egg. *Malva* is used like spinach but is consumed much less in Central America than in parts of Mexico. *Malva* is the most nutritious plant food found to date anywhere in the world, but has the misfortune of being the least palatable.

From the results of determinations of 14 nutrients in each of 1500 samples representing 250 varieties of edible plants collected in Mexico and Central America, the following conclusions have been reached: (a) the composition and nutritional values of plants grown in different regions are not the same; (b) tropical and semitropical plants are often highly nutritious; (c) man can formulate his diet from a wide variety of foods; (d) peoples with well-established cultures generally use indigenous resources intelligently; (e) there are more varieties of edible foods in Central America than in the United States; (f) indigenous foods are less expensive; and (g) the attack on the food problems of undeveloped areas must be realistic (R. S. Harris *Internat. Review of Vitamin Res.* 23: 3, 1952).

Although some of the plant foods in Central America and Mexico may be abundant in vitamins and adequate in essential mineral elements, it still needs to be demonstrated that with an intelligent selection of their indigenous plant flora they supply proteins of good quality for optimum physiological well-being, since such countries have inadequate supplies of foods of animal origin, such as meats, milk and eggs for bouyant health.

Certainly, their low life expectancy may be correlated with their subsistence largely on plant foods which, with the exception of the soybean, are of low biological value. Perhaps introduction of more extensive cultivation of the soybean in crop rotation with corn in regions where soil and geographic conditions permit, would materially improve the nutritional status of the people in Central America and Mexico.—B. SURE

The Food of the Australian Aboriginal. G. H. Bourne. *Proc. Brit. Nutrition Soc.* 12: 58, 1953.

The Australian aboriginal is a nomadic hunter and makes no attempt to cultivate the ground and to make permanent camps or settlements in any one place. A tribe will occupy an area of country until it is denuded of food and will then move on to a fresh region. In some areas food may be so plentiful that a tribe may remain there for considerable time. Since the advent of the white man and his establishment of sheep and cattle stations and of missions, groups of natives have tended to camp in the neighborhood of such settlements. Some were employed on the stations and were given mainly food in return for their labor, which consisted largely of white flour and sugar. When the natives had exhausted the natural foods and attempted to exist on these high-energy foods they developed marked

evidences of various vitamin-deficiency diseases.

During 1951 the Australian Government authorized an investigation into the diets of the natives living in contact with white people. The diets were investigated for calories, proteins, calcium, iron, vitamin A, thiamine and ascorbic acid. It was found that in general they were adequate in calories, proteins, iron, and thiamine. Many, however, were deficient in calcium, vitamin A, and ascorbic acid. The Government then recommended the type and amount of various foodstuffs for distribution to natives. Among the general recommendations was that liver and kidneys, instead of being fed to poultry, should be given to natives.

There are few creatures in the animal world which the Australian aboriginal does not use for food, but a more limited number of vegetable substances seems to be eaten. The men are concerned only in the hunting of large animals that require special skill or knowledge to find. Women collect plants and animals that can be obtained by hand work, such as digging, e.g. wombats, lizards, snakes, and snails. Frogs are collected mainly by women. Many sea fish are consumed by the coastal tribes and the northern tribes eat river fish.

Many birds are eaten, which include turkeys, ducks, pigeons, cockatoos, black swans, geese, hawks, and doves. Eggs are cooked by placing on hot ashes and turning frequently to insure even cooking.

Crabs, crayfish, and oysters are consumed by the coastal tribes. Mussels are also eaten by those living near rivers. Larger forms of snails are eaten, particularly by inland tribes. The pupas of ants represents another staple food and white ants are mixed with ground seeds and baked. Some types of moth are also very popular and when roasted taste like unpeeled almonds. In some parts of the country the natives periodically feast on moths. A fire is lit at night and as the moths are attracted they are thrown into the hot ashes and then consumed. Their juice is described as being of a rich yellow color. These feasts notably provide abundant vitamin A. Many caterpillars, particularly the green ones, are popular. They are flung into the hot ashes until they straighten out by which time the hairs are also singed off, and the animal is eaten. Many forms of larva are also eaten, the most popular being the big *Carsus* moth, known as the Witchedy grub.

Food taboos: Tribes bear the totem of various animals and some tribes are not allowed to eat the flesh of the animal whose totem name they bear. Expectant mothers in some tribes are not allowed to eat certain birds, snakes or grubs, and boys are not allowed to eat guannas (lizards) caught by day. In another tribe, no young girl may eat turkey, kangaroo, turtle, or turtle eggs, unless given to her by a young man.—B. SURE

The Diet of Canadian Indians and Eskimos. H. M. Sinclair. *Proc. Brit. Nutrition Soc.* 12: 69, 1953.

The Eskimos frequently eat their food raw, whereas such food habits disgust the Indians. The Eskimos live mainly north of the tree line, and although they collect some driftwood for sledges and boats, they depend mainly upon animals, snow, and rock for their houses, implements, boats, fuel, and clothing, while the Indians have access to wood for housing, boats, and fuel.

The Foodstuffs of the Eskimos

Winter: The entire food throughout the winter is the seal, which provides large quantities of superb fuel for lighting or heating. A 200-lb. seal provides nearly a 100 lb. blubber for winter. It is excellent food for men and dogs. Its skin is used for boats, clothing, and containers for oil. Its sinews are used for thread, and the intestines are used for clothing and windows. The Eskimo eats the greater part of the seal, including the blood. The meat, which is very dark, is very much relished.

Spring: The walrus, belonging to the same suborder as the seal, and the polar bear constitute the main source of food during the spring. The polar bear, which comes in from the pack ice to eat young seals, is hunted with dog-sledges and brought to bay by releasing the dogs. Its liver is not eaten by Eskimo or dog because it is toxic, apparently because of its great abundance in vitamin A, which produces hypervitaminosis.

Summer: With the arrival of summer, the dietary changes. Vegetation sprouts, and the Eskimo moves inland to hunt land animals, particularly the caribou. Fishing, especially for salmon, is important. Some berries are eaten. The commonest are the black crowberry, the dwarf blueberry, and cloudberry. Certain roots, the stalk of the aromatic angelica, some algae, and also the buds and young leaves of the dwarf willow are eaten in small amounts.

It may be concluded that, provided the Eskimo can catch his normal source of food, his diet is adequate. When the animals are scarce, or conditions such as fog prevent hunting, he often starves. It is generally agreed that rickets and scurvy are unknown. There is no evidence that the high protein diet causes any ill health. However, the Eskimo is very susceptible to infectious diseases, notably tuberculosis. Parasitism, including trichinosis, is extremely common.

The Foodstuffs of the Indians

The Indians extend over a wide area. Some, as the Iroquois and Hurons, were agricultural. Some—for instance, the Ojibwa—lived in the central forest area on deer, berries, and nuts. The Athabascans lived entirely on caribou, and the Blackfoot of the Plains on bison (buffalo). The Cree lived partly in the Plains on bison and antelope, and partly on caribou, moose, beaver, bear, and hares. Their downfall has been completed by the introduction of the dietary of our Western civilization: flour, sodium bicarbonate,

lard, sugar, and tea. The former three ingredients are united in haphazard proportions and baked into bannock.

The Eskimos used to subsist on a carnivorous diet, eating meat raw or lightly cooked with sea water, and consuming heads, skin, viscera, marrow, blood, and stomach contents. This was an excellent dietary in all respects, only failing when the hunting of seals or other animals was prevented. Despite almost complete lack of hygiene, they enjoyed a healthy happy life. The Bush Indians fared similarly upon cooked meat with some berries and nuts. The introduction of the white man's diet, in return for his exploitation of the furs and the extermination of the buffalo, changed matters. The Indian has so far been most affected, but wherever the Eskimo partakes largely of the white man's diet, the diseases of civilization follow. The life expectancy among the Eskimos in north Greenland is only about 26 years. Tuberculosis is responsible for nearly half the deaths of Eskimos and Indians in Alaska and is prevalent elsewhere. Other diseases which are common are arteriosclerosis and diabetes. Fortunately, the Danish, Canadian, and U. S. Governments have taken active steps to study and protect these peoples.—B. SURE

The Nutrition of Nigerian Peasants, with Special Reference to the Effects of Deficiencies of the Vitamin B Complex, Vitamin A and Animal Protein. B. M. Nicol. *Brit. J. Nutrition* 6: 34, 1952.

A report is given of a nutritional survey carried out in Southern Nigeria in 1949 and 1950. All food eaten was weighed and measured for three periods of 7 days throughout the years 1949 and 1950. Three typical families in three areas were selected for study. Only individuals considered to be 12 years or over were included in this investigation. The periods of study selected were in accordance with seasonal availability of staple foodstuffs.

The staple foodstuffs of the farmers and fishermen in the Southern areas are cassava and yam. The fishermen eat large amounts of fish, but the farmers eat small quantities of fish and supplement their protein ration with meat from small land animals, i.e., porcupine, pangolin, monkey, and snails. Pulses are used in small quantities by farmers. Apart from peppers, fresh vegetables are seldom cultivated by the peasants in Warri province. Fruit is seldom, if ever, eaten. Palm oil is plentiful and is the only cooking fat. Palm oil is the main beverage used by farmers.

A clinical examination of all the individuals whose diets were measured was carried out in each area.

The incidence of hepatic disease and anemia, which is almost always hypochromic and microcytic in type, was high, but the major nutritional diseases, beriberi, pellagra, and scurvy have not been encountered. The high rate of intestinal infestations, particularly with hookworms, round-worms, and shistosomes, was considered to be a more important factor in the production of anemias than dietary diseases.

The clinical symptoms of increased vascularity of the conjunctiva, angular stomatitis, and nasolabial seborrhea suggested riboflavin deficiency, and lesions of the tongue, together with the nature of the diets, indicated a nicotinic acid deficiency.

The dryness and depigmentation of the hair, general xerosis, follicular hyperkeratosis, "elephant skin," "crackled" skin, and night blindness indicated vitamin A deficiency. Although the diet of the Nigerian tribes contains ample quantities of carotene, it is possible they were unable to utilize vitamin A as a result of disturbed liver function or were low in fat to aid absorption of carotene.

The daily intake of thiamine was 1.02 mg. and that of riboflavin, 1.37 mg. to cover all physiological requirements, amounts which are entirely inadequate for optimum nutrition.

Consideration of the mean weights and nutrient composition of the diets of samples of the Nigerian population was taken to indicate the deficiency of the "animal protein" factor, which is probably vitamin B_{12}.—B. SURE

DIETARY STUDIES

There are many difficulties encountered in the analysis of the nutritional intake of individuals. The usual method employed by the physician is that of asking the patient to recall the items of food ingested in the recent past. For purposes of detailed study, this is obviously an unsatisfactory procedure. A more accurate approach to this type of study, together with the results achieved through instruction in nutritional needs, is reported.

Nutritional Status of Ten Family Groups in Washington State. O. M. Wilson and N. C. Esselbaugh. *J. Am. Dietet. A.* 28: 1133, 1952.

This reports a study designed to test the effect of nutrition education on the food habits of families. Ten families were selected on the basis of family composition, occupation of father, interest in the study, adequate income, and good health. These were divided into two groups, the *control* group of four families (19 persons) who received no nutrition education and the *experimental group* of six families (29 persons) who received instruction on nutritional needs and information on food purchasing, storage, preparation, and consumption. Education was given by individual help through a bi-weekly home visit to each family and by group meetings with the homemakers.

One-week records of weighed food intakes recorded by the housewife at the beginning and end of the study (November 1949–November 1950) were calculated for nutrient content. Eleven nutrients—calories, protein, calcium, phosphorus, iron, vitamin A, thiamine, riboflavin, niacin, ascorbic acid, and

vitamin D—were estimated. Each person's diet was classified as good, fair, or poor according to the number of these nutrients meeting or exceeding the National Research Council allowance. For good diets, this number was 9 or more; fair, 5–8; and poor, less than 5.

When the control and experimental groups were compared on the basis of the percentage of persons consuming good, fair, or poor diets at the beginning and end of the study, it was found that in the control 21, 42.1, and 36.8 per cent had good, fair, and poor diets respectively at the beginning, and 15.8, 36.8, and 47.4 per cent at the end. Similar data for the experimental group were 20.7, 48.3, and 31.0 per cent at the beginning and 55.2, 17.2, and 27.6 per cent at the end. Thus there was a shift in the control group from fair to poor diets and in the experimental from fair to good.

The initial food records showed that a large percentage of persons in both the control and experimental groups were receiving recommended allowances of protein, vitamin A, and niacin. A low percentage was meeting recommendations for calories, calcium, ascorbic acid, and vitamin D. These findings concur with data from surveys of other populations except for vitamin A, which more generally has been found low.

The authors conclude as a result of this study that the experimental families showed a consistent improvement in food patterns and overall conformity to the National Research Council standards for specific nutrients, whereas control families showed very little improvement. From the data presented, however, it is impossible to tell whether the differences are statistically significant since there is no description of the variation of the means.—J. M. Smith

Recognition has been given to the marked variation in food intake over long periods of time. Because of this fact, what may seem to be a deficient intake over one interval may not represent the true nutritional state, a matter which only a longer survey would reveal.

Dietary Surveys: Variation in the Weekly Intake of Nutrients. J. Yudkin. *Brit. J. Nutrition* 5: 177, 1951.

This paper deals with some of the limitations in methods of determining dietary intakes, and more particularly with the week-to-week variation in intakes.

The diets of 6 young women were studied for 4 consecutive weeks and, in two instances, for 1 further week after a short interval. The food was weighed by each subject and the calories and nutrients in them were calculated from food tables. The weekly intake of calories and nutrients showed marked variations. The extent of the variation differed with the various dietary ingredients and with the different subjects. For instance, in the week of highest food consumption, one subject ate 2 per cent more calories than in the week of lowest intake, whereas another took 68 per cent more calories. With vitamin A, the values in the highest week, were from two to five times as much as those in the lowest week. It is, therefore, possible for an individual to consume any of the dietary components which is adequate in one week, insufficient in another. The authors conclude that a 7-day dietary survey cannot be considered to give a sufficiently accurate assessment of the average intake of calories or nutrients by an individual.—B. Sure

The success of metabolic balance studies depends largely upon the accuracy of the measurement of the nutritional intake. The important factors involved in the dietary aspects of balance studies are considered in the following paper.

Dietary Techniques for Metabolic Balance Studies. A. G. Sampson, R. G. Sprague, and E. E. Wollaeger. *J. Am. Dietet. A.* 28: 912, 1952.

This paper presents a brief discussion of the principles involved in balance studies and describes *in detail* dietary techniques used in the metabolism unit of the Mayo Foundation and Mayo Clinic at St. Mary's Hospital. This information would be of value to anyone planning the dietary aspects of a balance study.

The authors consider this type of study of value in the investigation of the metabolism of the human organism in health and disease. Studies of nitrogen, carbon, sulfur, mineral, electrolyte, and water balance are suggested for this technique. In balance studies, diets must be individually planned to meet the requirements of the particular investigation and to supply nutritional requirements as they vary with sex, age, height, and physical activity.

Foods should be chosen which undergo minimal change during preparation or storage and they should be prepared in uniform manner throughout the study. The patient's eating habits should be considered in choosing foods. He is given careful instruction in the technique and purpose of the study before starting and is permitted some practice before data are recorded. Insofar as possible, all foods for the study are purchased in advance from a uniform source and stored under uniform conditions until ready for use. Food is weighed on a torsion balance accurate to 0.1 Gm. Procedures employed in selection and preparation of foods are given in detail in the paper.

The authors emphasize the importance of the dietary portion of balance studies, since the research is worthless unless the dietary is accurately prepared. The palatability of the diet and the sensitivity of the dietitian to the needs of the patient are largely responsible for the type of cooperation received. The total success requires cooperation of all members of the research team: physician, nurse, dietitian, kitchen

helper, biochemist, and laboratory technician, as well as the patient.—J. M. SMITH

The results obtained in a study in which careful analysis was made of the nutritional intake with respect to nitrogen and of the losses of this substance by various routes revealed a mean retention of 0.64 Gm. per day. This value was obtained from apparently normal diets comprising the usual foods.

The Amount of Nitrogen Retained by 6 Young Women on an Intake of Approximately 70 gm of Protein a Day. F. A. Johnston and T. J. McMillan. *J. Nutrition* 47: 425, 1952.

Of the 6 subjects in this study, 5 were from 20 through 23 years of age, and 1 was 31 years old. Their mean body size and height were comparable to that of the population group of 1661 women from 20 through 24 years of age measured by the Bureau of Home Economics and reported in 1941. The menus, made up of a variety of common foods, were planned on a weekly basis and repeated 12 times. The weights of all the foods used by each subject were recorded and analyses were made for those containing nitrogen. Weekly composites of food, feces, and urine were made. The urine was preserved with HCl without heat treatment. Tampons used for the collection of menses were digested with HCl. The amount of nitrogen in the coffee and cola drinks was determined and subtracted from the total urinary nitrogen, because the nitrogen in these beverages is not available for use by the body.

The mean intake of protein on the basal diet was 67.0 Gm., on the diet containing spinach, 71.8 Gm., and on both diets for all 12 weeks, 70.2 Gm. The mean amount of nitrogen retained by the 6 subjects during 12 weeks was 0.64 Gm. per day, or 0.61 Gm., if the loss of nitrogen in the menses was deducted. The amount retained varied widely from week to week for a given subject, but the means for 12 weeks were similar for all subjects. A satisfactory amount of nitrogen was retained despite the omission of all animal protein from breakfast. Approximately 91 per cent of the nitrogen of spinach was absorbed.—B. SURE

Nitrogen balance studies performed on subjects accustomed to marginal diets disclosed that the reduced requirements in chronic malnutrition were satisfied by nitrogen intakes smaller than those of well-nourished individuals.

Nitrogen Metabolism in West African Children. B. Bray. *Brit. J. Nutrition* 7: 3, 1953.

Very few nitrogen balance studies have been reported on human subjects whose diet is habitually on the margin between adequacy and starvation. The experiments described in this paper were performed in order to determine the nitrogen metabolism in African children and then, by comparison with American data, to ascertain whether there is any difference in nitrogen economy between individuals accustomed to a poor and to a full diet.

A series of nitrogen balances was carried out in the Gambia on 8 West African boys, aged 7 to 9 years. No consistent change in the balance of nitrogen metabolism was found after the elimination of the parasites *Ascaris lumbricoides* and *Ankylostoma duodenale*. The proportion of dietary nitrogen lost in the feces was higher than in American children of similar chronological age. The total urinary nitrogen was low compared with that of American children, with a lower proportion of urea and a higher proportion of ammonia. The reduced urinary nitrogen resulted in a larger retention on a smaller intake than in American children. Balance data confirmed clinical observations on retarded development. The reduced requirements of chronically malnourished Gambian children were satisfied by intakes smaller than those of American children of the same age. Retention of nitrogen was not accompanied by a corresponding increase in body weight under the conditions of this test. At present there is no explanation of this observation.—B. SURE

The effect of starvation upon normal subjects has been extensively investigated. The biochemical, physiological, and psychological alterations associated with undernutrition have been recorded by Keys, Brožek, et al. (also see J. CLIN. NUTRITION 1: 107, 1953).

Starvation and Nutritional Rehabilitation. J. Brožek. *J. Am. Dietet. A.* 28: 917, 1952.

This reports a case study of one of 32 subjects who participated in an extensive study of morphologic, biochemical, physiologic, and psychologic characteristics during starvation and rehabilitation. According to the author, this typical subject provides a fairly satisfactory picture of alterations which took place during semistarvation, but is definitely inadequate for a portrayal of the period of nutritional rehabilitation, which demands an intricate statistical analysis based on data for all 32 subjects.

The experimental regime consisted of a 12-week control period on a control diet (3900 cal.); 24 weeks of semistarvation (1470 cal.); 12 weeks restricted rehabilitation (approximately 3000 cal.) and 8 weeks unrestricted (6000–6500 cal.). The starvation diet was composed of types of foods likely to be available in European famine areas. During the rehabilitation period, foods were merely increased in amount. The basal diet during starvation, modified in individual cases by altering the amount of bread and potatoes, contained 53.2 Gm. protein, 34.5 Gm. fat, and 295.0 Gm. carbohydrate. The vitamin content was: vitamin A, 1600 I.U.; thiamine, 1.29 mg.; riboflavin, 0.60 mg.; niacin, 20.7 mg.; and ascorbic acid, 83 mg.

Data are given in detail for a subject 25 years of age, 181 cm. tall, weighing 64.7 Kg. at the beginning of the study. During semistarvation, body circumference decreased and weight declined approximately

19.5 per cent. Body fat showed higher mobility than fat-free body weight and density of selected bones showed no measurable change throughout the experiment. The amount of active tissues declined 23.2 per cent. Plasma protein concentration declined from 6.67 Gm./100 cc. to 5.8 Gm./1000, but total circulating protein showed a negligible change (202 Gm. initial to 197 Gm.). The authors consider circulating hemoglobin a much more sensitive indicator of the altered nutriture—initial values 737 Gm., final 477. The number of red and white blood cells decreased markedly in starvation and rose slowly during recovery. Blood cholesterol declined 40 mg. (initial 200 mg./100 cc.) during the starvation period.

Urinary nitrogen declined from 12.1 Gm./24 hrs. to 7.5 during starvation and rose slowly to 10.5 at the 12th week of rehabilitation. Nitrogen balance data are not reported. Marked polyuria was noted. This persisted beyond the 12th week of rehabilitation.

Basal metabolism decreased from 1467 cal./24 hrs. to 894 at the end of semistarvation, rose slowly during 12 weeks of rehabilitation (1229 cal./24 hrs.), and increased dramatically during the first week of unrestricted intake. Expressed in cal./Kg. active tissues, the above values were 37.0, 29.3, and 38.4. Assuming energy equilibrium, the cal./24 hrs. used for physical activity were 2137 and 482 at the end of the control and semistarvation periods respectively.

Detailed analysis of cardiovascular changes during semistarvation revealed bradycardia, hypotension, decrease in skin temperature, slight grayish-blue tinge of the skin, dizziness, and blackouts.

The special senses were remarkably resistant to caloric deficiency. Visual acuity showed small random fluctuations, flicker fusion frequency showed a statistically significant but biologically unimportant decrement. Auditory acuity increased.

Four aspects of voluntary motor performance—strength, speed, coordination, and endurance, were affected unequally by the dietary regime. Strength, measured by hand grip and back lift, showed a definite and biologically important decrease. Speed, measured by reaction to visual stimuli or speed of tapping, did not change appreciably. Profound alterations were found in the subject's endurance, as measured by ability to run on a motor-driven treadmill. This decline was more rapid than for strength of grip, and recovery was slower.

The intellective capacity, measured both by tests which were short and limited in time and long tests with no time limit, showed no decline in the speed tests but a definite decrease in a test requiring a good deal of sustained attention.

Personality changes were marked and can be labeled as "semistarvation neurosis." The Minnesota Multiphasic Personality Inventory revealed deviations toward hypochondriosis, depression, and hysteria. Some changes were noted on the psychotic scale, especially schizophrenia.—J. M. SMITH

ITEMS OF GENERAL INTEREST

A number of interesting observations on nutritional therapy and basic physiology have recently appeared. The following are a few "items of general interest."

Dietary Treatment of Hypertension. III. The Effect of Protein on Appetite and Weight. V. P. Dole, L. K. Dahl, I. L. Schwartz, G. C. Cotzias, J. H. Thaysen, and C. Harris. *J. Clin. Investigation* 32: 185, 1953.

This study was carried out in order to discover what dietary factor was responsible for the weight loss which occurs when patients are shifted from a conventional diet to a rice diet low in sodium and protein. Six patients with hypertension were studied. The basal diet contained 4 ± 1 mEq. of sodium and 35 ± 5 Gm. of protein per day. When increased amounts of sodium were desired, capsules of sodium chloride provided 10 Gm. of added salt. Extra protein was supplied as Lesofac ® (Wyeth, Inc.). A period on 1.5 Gm. of protein/Kg. and 175 mEq. sodium was followed by successive periods of low sodium, normal protein intake; low sodium, low protein intake; low sodium, extremely low protein intake; and finally low sodium, normal protein intake. It was apparent that appetite and weight were directly dependent upon the protein intake and that 1 Gm. of protein accounted for the intake of 14.6 calories in extra nonprotein foods. This figure is well above what can be accounted for by the specific dynamic action of protein.

The protein level had no influence on the hypertension. Only the sodium content of the diet affected this factor and weight gain or loss had no direct effect.

These results show that appetite and body weight can be controlled under some conditions by changes in the amount of dietary protein. The reviewer cannot agree with the authors, however, in the statement that the low protein diets were adequate. Dietary adequacy cannot be determined by (1) maintenance of nitrogen balance, (2) maintenance of weight, or (3) the fact that a large number of people in the world subsist and reproduce on such diets. The homeostatic mechanisms of the body are so adaptable that on a very low intake of an essential nutrient, intake and output may balance even while signs of deficiency disease are appearing. Weight may remain essentially steady during the same period and it is well known that a majority of the earth's inhabitants are inadequately fed.—R. W. VILTER

Studies on the Establishment of a Low-Sodium-High-Protein Dietary Regime: A Simple Method for the Removal of Sodium from Eggs. I. S. Kleiner, G. G. Ornstein, H. Baron, A. Katchman, U. Batzdorf, and E. P. Ajemian. *Bull. New York Med. Coll.* 15: 91, 1952.

Eggs contain a high percentage of protein of ex-

cellent quality and are almost indispensable in cooking. The relatively high sodium content of eggs makes the possibility of a "low-sodium egg" desirable. The authors describe a method in which eggs are mixed in a Waring blendor until homogeneous. They are then transferred to a dialyzing membrane which is suspended in a large volume of tap water or distilled water, and this is placed in the refrigerator and preferably kept in constant motion. After a suitable length of time (and the amount of sodium removed depends in part on the time in which the material is dialyzed), the eggs are removed and may be used directly for cooking or may be lyophilized. In the reported series of experiments, over 60 per cent of the sodium, and somewhat more of the potassium, was removed after a period of 4 to 24 hours. Thus, on a wet basis, an egg containing 65 mg. of sodium retained only 22 mg. after 24-hour dialysis.—S. O. WAIFE

Metabolic and Clinical Effects of Different Regimens in Patients with Chronic Liver Disease. G. R. Morly, C. R. Paynter, C. F. Consolazio, and R. M. Kark. *Metabolism* 1: 314, 1952.

This is a detailed report of clinical, metabolic, and laboratory data on 4 patients with cirrhosis of the liver who were studied for 126 days while subsisting on four different therapeutic regimens.

From careful clinical observations it appears that the greatest improvement occurred during and shortly after therapy with the control regimen plus intravenous administration of an amino acid mixture. No additional advantage accrued from supplementing the high protein diet with cystine and choline, methionine, vitamin B complex orally with liver extract intravenously or human serum albumin in addition to the foregoing. The control diet was composed of two times the basal caloric requirement, 2.5 Gm. protein/Kg. of body weight, fat composing 30 per cent of total calories, and only 0.9 Gm. of sodium a day. Although a cirrhotic patient will generally improve on a "well-balanced" low salt diet, devoid of alcohol, the high protein intake (2.5/Kg.) increased the rate of repair as measured by weight gain and nitrogen retention. The administration of 120 Gm. of amino acids a day (as a 10 per cent solution intravenously) aided the recovery process. It is significant that serum protein levels did not change, although these patients stored large amounts of protein, no doubt as new tissue.

Of six liver function tests repeated at frequent intervals during the study, the serum cholinesterase activity correlated best with changes in the patients' clinical condition.

The authors rightfully conclude that intensive and prolonged high protein therapy is necessary in patients with cirrhosis of the liver.—S. O. WAIFE

Effects of Diets on Uric Acid Excretion. D. Wilson, C. Bishop, and J. H. Talbott. *J. Applied Physiol.* 4: 560, 1952.

These experiments were performed with an adequate method for urinary uric acid (isotope dilution) and good control over the subjects for an extended period of time. Daily variations in uric acid excretion were measured involving the simultaneous shifting of several variables and with no assumption as to constancy in regard to the subjects or time. Protein, fat, carbohydrate, or purine-rich protein were added to basic diets. Significantly more uric acid was excreted while ingesting purine-rich protein. More uric acid was excreted on a high protein than on a high fat diet. One hour of vigorous exercise did not affect uric acid excretion.—M. J. OPPENHEIMER

Forced High-Calorie Low-Protein Diet in the Treatment of Uremia. W. J. Kolff. *Ann. New York Acad. Sc.* 56: 107, 1952.

There is experimental evidence that protein deleteriously affects the course of uremia. Since high-caloric feeding has a protein sparing action, the author treated 33 patients with renal insufficiency and uremia with various high calorie regimes. Twenty-one received a vegetable oil emulsion containing sucrose. Twelve were able to take the mixture for some time and had a fall in blood urea or showed clinical improvement. Seventeen subjects received 20 per cent invert sugar intravenously with "success" in seven.

In chronic uremia, the adequacy of dietary control usually can be estimated from the urine urea output. If adequate nonprotein calories are administered, the protein intake may safely be reduced to 20 Gm. daily. The possibility of potassium depletion or the development of avitaminoses under this regimen must be kept in mind. Unfortunately, a comparable series of patients receiving isocaloric diets, with variable protein intakes, is not presented.

Although little should be expected from dietotherapy alone in uremia, the potentiality of favorably influencing the course of renal insufficiency by diet deserves further attention.—S. O. WAIFE

Treatment of Multiple Sclerosis with Low-Fat Diet. R. L. Swank. *Arch. Neurol. & Psych.* 69: 91, 1953.

The author had previously suggested that the incidence of multiple sclerosis was related to the amount of fat consumed in the general population, and that the consumption of relatively saturated milk and animal fats is more likely to be associated with the high incidence of multiple sclerosis than the consumption of unsaturated vegetable and fish oils. This report is based on 47 patients who have been on a low fat diet for 2 to 3½ years or more. Patients acted as their own controls in relating the frequency and severity of exacerbations to dietary intake. The caloric intake averaged about 1700 calories for a woman and 1900 calories for a man, and a protein intake at about 50 Gm. or more a day. A multivitamin capsule was used for supplementation. Skimmed

milk was used as a source of protein, and most patients ate at least one egg a day. The dietary intake of the patients was checked at 2-week intervals by means of a dietary history. The diet recommended at present contains less than 40 Gm. of fat. It consists of about 20 cc. of hard fats (animal fat, margarine, lard, and shortening) and 4 teaspoonfuls, or 20 cc., of vegetable oil or a substitute. In addition, 5 cc. of cod liver oil is given daily.

Foods which are forbidden include whole milk, butter, cream, and foods containing these substances, such as pastries, pies, cakes, cookies, chocolate, ice cream, etc.

The author feels that this diet was beneficial to a large percentage of the 47 patients, particularly in those in whom the disease was in early phase. The reduction in severity and frequency of exacerbations was substantial. A further study will be necessary to evaluate the final position of a low fat diet in the therapeutic regimen. The hypothesis is stated that patients with multiple sclerosis have a basic defect in the suspension stability of their blood which is upset by the hyperlipemia following heavy meals. The difficulties in controlling a study of this type are stated, and it was necessary to compare the pretreatment and treatment course of the disease, which at best is only partially satisfactory.—S. O. WAIFE

Inhibition of the Clot-Accelerating Property of Ingested Fat by Simultaneous Feeding of Sugar. J. M. Waldron, B. Beidleman and G. G. Duncan. *J. Applied Physiol.* 4: 761, 1952.

When cream or refined corn oil is fed to human subjects the coagulability of blood is increased. Addition of sucrose or lactose to the intake along with the fat did not decrease clotting time as much as with fat alone. The authors showed that the sugars studied did not have anticoagulant properties, since when fed alone clotting was accelerated. The possibility is indicated that the transport of fat is altered during the simultaneous transport of sugar.—M. J. OPPENHEIMER

Effects of Dietary Protein and Methionine on the X-Irradiated Rat. W. W. Smith, I. B. Ackerman, and I. M. Alderman. *Am. J. Physiol.* 169: 491, 1952.

Rats were irradiated at values of 550 r. The death rate was a little higher among those who were maintained on a 6 per cent casein diet than those who received 18 and 35 per cent casein diets. It did not matter in the 40-day mortality if the casein in the diet was reduced after irradiation. Increase of casein to 60 per cent led to a statistically insignificant reduction in mortality. Methionine and cystine added to low protein diets produced no change. X-irradiation depression of red and white cell production was scarcely influenced by diet. There was a small delay in the reduction of circulating reticulocytes when the casein was 35 per cent of the diet. Oxygen use was decreased in anesthetized rats on 6 per cent casein and increased by 60 per cent casein when compared to animals on 18 per cent casein in their diet.—M. J. OPPENHEIMER

The Protective Effect Against X-Irradiation of Methyl Lineolate in the Rat. H. J. Duell, Jr., A. L. S. Cheng, G. D. Kryder, and M. E. Bingemann. *Science* 117: 254, 1953.

It had previously been found that rats receiving a small amount of cotton-seed oil in the diet were more resistant to injury from x-irradiation than animals on a fat-free regimen. This report shows that the increased survival time of rats receiving 10 mg. of methyl lineolate daily is significantly greater than that of rats receiving the basal fat-free diet without lineolate. The reason for the beneficial effect of methyl lineolate in radiation injury is not clear. Probably it is related to the metabolism of the epidermis, since a number of other substances also efficacious in irradiation injury, such as cystine, ascorbic acid, and vitamin P, are also involved in epidermal metabolism.—S. O. WAIFE

The Serum Chemistry in Uncomplicated Kwashiorkor. R. F. A. Dean and R. Schwartz. *Brit. J. Nutrition* 7: 131, 1953.

Although the literature of kwashiorkor is now reaching large dimensions, few studies of the serum chemistry have so far appeared. There has been up to now no general agreement on diagnostic criteria, and the name kwashiorkor or one of its synonyms has undoubtedly been applied to diverse conditions arising from various causes in different parts of the world. The disease as it is seen at Mulago is often complicated by other illness. It was, however, possible to select a group of children in whom the state of malnutrition was dominant, and the results were obtained from this group.

The children were either of the Baganda tribe or belonged to other tribes who, settled in Kampala or its vicinity, had adopted the feeding habits of the Baganda. In this tribe the most popular food is the cooked banana. The staple next in popularity is the sweet potato. If this cannot be obtained, maize flour or cassava may be eaten. All these foods are cooked with water. The green leaves of plants are often cooked with the other ingredients of the diet. The beans must make a valuable contribution to the total protein of the diet, but the supply is seasonal and the price is high in relation to that of the other foods. The value of the green leaves is almost entirely due to their vitamins and minerals and not to their protein content. It is difficult to see how a child in the first years of life, whose capacity for bulky food is necessarily small, can possibly obtain from such a diet more than 10 to 15 Gm. protein daily, and there can be no assurance that the mixture of proteins in the diet will provide an adequate mixture of amino acids.

The outstanding features of the results seem to be

the low levels of albumin and blood urea in the serum of the children on admission, the low levels of enzyme activity at that time, and the rapid rise of all these levels toward normal when therapy with large amounts of milk protein was begun. Treatment with large amounts of milk protein rapidly caused alterations in the blood, which coincided with alterations in the contents of the duodenal juice, and with improvements in the clinical condition of the children.—B. SURE

Rickets and Amino-Aciduria. J. H. P. Jonxis, P. A. Smith, and T. H. J. Huisman. *Lancet* 2: 1015, 1952.

The excretion of free amino acids and of peptides and of conjugates by children with florid rickets was much greater than normal. During recovery, excretion of both free and bound amino acids decreased. These changes occurred more slowly than changes in serum calcium and phosphorus levels. Evidence of previous rickets and of abnormally high concentrations of amino acids in the urine was also found in members of a family of a patient with rickets. Indications at present are that the level of amino acid nitrogen in the plasma of these patients is within the normal range, and this suggests that the renal threshold may be reduced in rickets.—S. O. WAIFE

The Influence of Various Sources of Nitrogen on the Activity of Antimicrobial Drugs. II. Mycobacterium avium. *Am. Rev. Tuberc.* 67: 503, 1953.

Although other investigators have presented evidence that penicillin and bacitracin may interfere with the uptake of certain amino acids by *Micrococcus,* the author has previously shown that such is not the case with *Serratia* organisms which do not require preformed amino acids for anabolism. The present paper reports similar results for a rapidly growing strain of *Mycobacterium avium.* This organism, like *Serratia,* is resistant to penicillin, whereas the *Micrococcus* is susceptible to this drug. These facts suggest that bacterial inhibition by penicillin occurs only when the organism requires preformed amino acids for growth, but information to support this hypothesis is at present incomplete. With respect to the inhibition of *M. avium* by other antibiotics such as bacitracin, chloramphenicol, streptomycin, aureomycin, and terramycin, there was no influence by changes in the source of nitrogen, whether organic or inorganic.—W. WEISS

Basal Heat Production and Elimination of Thirteen Normal Women at Temperatures from 22° C. to 35° C. E. F. DuBois, F. G. Ebaugh, Jr., and J. D. Hardy. *J. Nutrition* 48: 257, 1952.

Seventy-six experiments in the Sage respiration calorimeter were made on 13 normal young women at environmental temperatures between 22° C. and 35° C.

The average basal metabolism of the 13 women was 31.2 cal./sq. m./hr. This is so much lower than the heat production of men per unit of surface that women have an advantage over men in the warm zones and do not need to sweat as much. In the cold zone some, but not all, women lose heat less rapidly than men.

In the cold zone the women lost about 67 per cent of their heat by radiation and this percentage dropped in linear fashion to zero when the calorimeter temperature was the same as skin temperature. Vaporization accounted for only 16–18 per cent of the total loss at the coldest temperatures and reached the conventional figures of 24-25 per cent only at environments of 27° C. to 26° C. It is obvious that fixed percentage figures for radiation, convection, and vaporization apply to only one strictly specified set of conditions.

The comfort or neutral zone for women, naked, and in strict basal conditions, extended from about 26° C. to 30.9° C. In this zone the average skin temperature was 33.9° C. and in the upper part of the zone heat production closely approximated heat elimination. Of the 10 women studied at temperatures of 28 and below, 6 showed an increase in metabolism in the cold greater than the amount that could be ascribed to muscle tension or restlessness. This is evidence that some, but not all, women are subject to Rubner's "chemical regulation" of metabolism, but the amount involved is small.

In the cold zone the peripheral tissues lost so much heat that the average temperature of the body dropped 2.8° C. before the onset of shivering. The metabolism of the peripheral tissues falls with lower temperatures. Since the total metabolism remains constant or rises, there must be an increase in the metabolism of the core of the body which compensates for the decrease in the periphery. In this sense there is a chemical regulation in men and women.—B. SURE

Basal Metabolism of the Eskimo. Kaare Rodahl. *J. Nutrition* 48: 359, 1952.

It has been claimed by several workers that there are distinct racial differences in basal metabolism. No satisfactory explanation has been offered for these differences. In connection with studies on human adaptation to cold which were in progress at the Arctic Aeromedical Laboratory, it was considered desirable to examine, under carefully controlled conditions, whether there is any difference in the basal heat production in Eskimos as compared with whites, and if so, how such a difference may be explained. On this basis, a series of comprehensive studies of basal metabolism has been carried out from 1950 to 1952 on a large number of Eskimos from various native settlements in Alaska.

Three hundred and forty basal metabolism tests have been made on 73 healthy Eskimos from 4 different locations in Alaska, together with environmental observations, body surface-area measurements,

and determination of protein intake and nitrogen elimination. In agreement with previous workers, the basal metabolism of Eskimos examined for the first time in their native habitat was significantly higher than in the whites. Approximately 9 per cent of this higher basal metabolism may be accounted for by apprehension, while the high protein Eskimo diet accounts for approximately 15 per cent. When these two factors were eliminated, the metabolism was almost exactly the same as in the white controls. From these studies, it is therefore concluded that there are no racial differences between the Eskimos and the whites in basal heat production.—B. SURE

Vitamin A Concentration in the Liver in the Nephrotic Syndrome. B. M. Kagan and E. Kaiser. *J. Lab. & Clin. Med.* 40: 12, 1952.

Liver tissue was obtained from patients who died of nephrotic syndrome, as well as from patients who died of other causes. The vitamin A content of the liver was measured following digestion of the tissue. The liver in nephrotic syndrome was found to contain concentrations of vitamin A considerably higher than those of the other groups studied. Previous work has demonstrated that the blood levels of vitamin A likewise are elevated in nephrosis.—C. R. SHUMAN

Metabolism of Women during the Reproductive Cycle. The Effect of Multi-Vitamin Supplements on the Secretion of B Vitamins in Human Milk. J. P. Pratt, B. M. Hamil, E. Z. Moyers, M. Kaucher, C. Roederuck, M. N. Coryell, S. Miller, H. H. Williams, and I. G. Macy. *J. Nutrition* 44: 141, 1951.

The present study was undertaken to investigate the levels of thiamine, riboflavin, niacin, pantothenic acid, and biotin in the milk and urine of nursing mothers: (1) while they were taking the same foods in diets adjusted to meet physiologic needs and satisfy appetite; and (2) the corresponding rates of elimination of these vitamins in milk and urine after their self-chosen diets had been supplemented for 6 to 14 days with about 10 times the recommended daily allowances of thiamine, riboflavin, niacin, vitamin A, and vitamin C.

Ten mothers 21 to 35 years old participated in the study during one to four periods of observation after mature milk production was established. The vitamin content of their milk and urine was determined before and after ingestion of multivitamin supplements. Each of 18 studies consisted of control periods of five consecutive days followed by administration daily for 6 to 14 days of a supplement consisting of 750 mg. ascorbic acid, 50,000 I.U. vitamin A, 12 mg. thiamine chloride, 15 mg. riboflavin, and 120 mg. niacin in addition to an adequate diet. Results were obtained from analysis of 24-hour collections of food, breast milk, and urine for thiamine, riboflavin, niacin, pantothenic acid, and biotin.

The amounts of vitamin given did not stimulate milk production, since after supplementation equal numbers of studies showed increased and decreased volumes of milk. The mothers had a wide range of physiologic response to vitamin supplementation among individuals and for the same individual at different intervals in lactation.

The percentages of thiamine, riboflavin, and niacin intakes found in milk and urine increased with supplementation, though not consistently for all subjects nor in proportion to the increased intakes. The responses to pantothenic acid and biotin supplementation were negative.—B. SURE

The Relation of the Choline Cycle to Cardiac Decompensation: Acetylcholine Metabolism in the Dog Heart-Lung Preparation. W. M. Govier, W. A Freyburger, A. J. Gibbons, B. G. Howes, and E. Smits. *Am. Heart J.* 45: 122, 1953.

The hypothesis is offered that the choline cycle (acetylcholine $\xrightarrow{\text{cholinesterase}}$ choline + acetyl + energy) is essential for maintenance of cell wall permeability and integrity; interference with this cycle may be a key factor in the biochemical pathogenesis of myocardial failure. Cardiac failure, produced in atropinized dog heart-lung preparations by administration of pentobarbital, was often associated with decreased myocardial cholinesterase activity. Penicillin G, physostigmine or diisopropyl fluorophosphate—choline cycle inhibitors—also produced cardiac failure. Ouabain may have a positive inotropic effect in these decompensated preparations, accompanied by an increase in cholinesterase activity. Large doses of choline are also positively inotropic. These findings are interpreted as offering experimental support for the hypothesis propounded.—J. STAMLER

The Effect of Sublingual Administration of Crystalline Vitamin B_{12} in Tropical Sprue. R. M. Suarez, J. Sabater, R. M. Suarez, Jr., and R. Buso. *Blood* 7: 749, 1952.

These authors point out that though parenterally administered vitamin B_{12} has been effective in tropical sprue, oral administration of 25 μg. a day or single oral doses of 100, 500, or even 1000 μg. are ineffective. Good clinical responses have been obtained with a single dose of 3000 μg. and maximal responses with 5000 μg. Since certain drugs and hormones are readily absorbed when administered sublingually and have an action through this route which is as rapid and practically as effective as when given parenterally, these authors studied the effect of crystalline vitamin B_{12} administered sublingually to sprue patients. Their series consisted of five patients with all the diagnostic criteria of acute sprue and of sprue in relapse. Twenty-five μg. of vitamin B_{12} was given sublingually each day for a period of 10 days. No clinical or hematologic remission occurred in any of the patients. The authors conclude that the sublingual route of vitamin B_{12} administration is ineffective for the treatment of tropical sprue. —R. W. VILTER

A Comparison of Effect of Vitamin B_{12} with That of Liver Extract in the Treatment of Pernicious Anemia During Relapse and for Maintenance. W. P. Murphy and I. Howard. *New England J. Med.* 247: 838, 1952.

The clinical and hematological response to crystalline vitamin B_{12} of 8 patients with pernicious anemia in relapse was compared with the response of 20 patients with comparable initial erythrocyte levels who were treated in the same way except that refined liver extract was given intramuscularly in a dosage of one antipernicious-anemia-unit daily for 28 days. The ages and neural involvement of the two groups were similar. Although in general the clinical effect both during relapse and for maintenance has been similar to that observed with the use of liver extract, there was an almost uniformly greater increase in erythrocytes in patients treated with liver extract than in those who received vitamin B_{12}. The difference in rate of increase is most evident by comparison of the figures of the two groups. No patient receiving vitamin B_{12} reached a red cell level of 4,800,000 in the 28-day period, whereas 6 of those on liver extract reached this or a higher level; furthermore, about one-third of the vitamin B_{12}-treated patients reached blood red cell levels of 4,500,000 or higher, whereas two-thirds of the liver extract patients did so. There is evidence suggesting that one U.S.P. unit of liver extract is probably equivalent to about 1.3 μg. of vitamin B_{12}—not to 1μ. as was previously suggested. Furthermore, severe reactions, according to Murphy and Howard, following the use of refined liver extracts have been so rare that failure to observe them after B_{12} injections has not been impressive.—S. O. WAIFE

Daily Determination of Plasma, Serum and White Cell-platelet Ascorbic Acid in Relationship to the Excretion of Ascorbic and Homogentisic Acids by Adults Maintained on a Controlled Diet. B. L. Davey, Mei-Ling Wu, and C. A. Storvick. *J. Nutrition* 47: 341, 1952.

It was the purpose of this study to determine whether serum and plasma ascorbic acid values are the same and to determine whether total and reduced ascorbic acid values are the same in either serum or plasma. Four healthy adult women were placed for 52 days on a basal diet containing 1000 calories. Each subject chose two supplemental units, so that the diet for all subjects contained about 2000 cal. per day.

Ascorbic acid levels in the blood and urinary excretion of ascorbic acid and homogentisic acid equivalents showed similar changes for each of the four subjects receiving 25 mg. of ascorbic acid daily. The results indicate that a daily intake of 25 mg. ascorbic acid is not enough to maintain plasma or serum ascorbic acid at a generally accepted "good" level, i.e., 0.6–0.8 mg. per 100 ml. A daily intake of 75 mg. of ascorbic acid maintained levels of 0.84 mg. of total ascorbic acid per 100 ml.; 0.73 mg. of reduced ascorbic acid/100 ml. of serum, 0.66 mg. of total ascorbic acid/100 ml. of plasma, and 0.61 mg. of reduced ascorbic acid/100 ml. of plasma for one subject. White cell-platelet levels averaged 21.3 mg./100 ml.

There is no evidence from this study to indicate that there was any disturbance in tyrosine or phenylalanine metabolism as a result of lowered ascorbic acid intake. Urinary excretion of homogentisic acid was increased in none of the subjects studied. White cell-platelet ascorbic acid levels fell to half or less of initial values in the subjects ingesting 25 mg. of ascorbic acid daily.—B. SURE

Ascorbic Acid Nutrition in the Human. I. Tyrosine Metabolism and Blood Levels of Ascorbic Acid During Ascorbic Acid Depletion and Repletion. B. F. Steele, Ching-Hsiang Hsu, Z. H. Pierce, and H. H. Williams. *J. Nutrition* 48: 49, 1952.

This report is concerned with the urinary excretion of "tyrosyl" compounds and the ascorbic level of serum and white cells of 10 adult humans ingesting a diet containing 7 mg. or less of vitamin C. Five men and five women volunteered to serve as subjects. They ranged between 21 and 32 years of age and on the basis of medical examination were judged to be in good physical condition.

The menus were planned on a three-day basis and were repeated throughout the experimental period of 82 days. A diet consisting of eggs, beef, pork or fowl, milk, stewed prunes, and canned pears were eaten by each subject. Cereal products and butter were added in various amounts to meet each subject's energy needs. Sugar, special hard candies, and soft drinks were allowed *ad libitum* in known amounts. With the exception of ascorbic acid, the diet was considered to be adequate in known dietary essentials for the human. The daily intake of ascorbic acid was 15 mg. or less during the first two weeks. By treating the milk with heat, the ascorbic acid intake was reduced to 7 mg. or less per day during the remainder of the depletion period.

Average serum and white cell ascorbic acid values fell to 0.3 and 13 mg. per cent, respectively, at the end of 31 days of depletion. After 78 days they averaged 0.2 and 11.5 mg. per cent, respectively. These levels returned to normal when the subjects were repleted with 800 mg. of ascorbic acid daily for 4 days.

Of the 23 instances when serum values were less than 0.4 mg. per cent, only one white cell value was greater than 14 mg. per cent. When serum values greater than 0.4 mg. per cent were encountered (8 cases), no values under 14 mg. per cent were found for white cells.

On the basis of the results of this study, low blood serum ascorbic acid values (less than 0.4 mg. per cent) would indicate a past history of poor ascorbic acid nutriture and an inadequate or deficient intake of this vitamin.

There was an increase in the reducing power of the urine as the subjects became more depleted of ascorbic acid, but the urinary excretion of "tyrosyl" compounds and of reducing substances did not reach abnormal levels during the depletion period, even though 10 Gm. of free tyrosine were given orally to each subject during the 6 days of each metabolic period.—B. SURE

Ascorbic Acid and Acclimatization to Cold in Monkeys. L.-P. Dugal and G. Fortier. *J. Applied Physiol.* 4: 143, 1952.

These experiments demonstrated that monkeys do not resist intense cold (—20° C.) better if they were exposed to 10° C. for 6 months in advance and received 25 mg. of ascorbic acid daily than do controls kept at room temperature and receiving the same dose of ascorbic acid. However, if the amount of ascorbic acid is increased to 325 mg. daily and this is combined with preëxposure to mild cold (10° C.) for 6 months, then the monkeys are much more resistant to intense cold (—20° C.) than either controls at room temperature or controls at room temperature plus 25 mg. of ascorbic acid daily. Criteria used for resistance to cold was the ability to maintain rectal and intramuscular temperatures in suddenly applied environmental temperatures of —20° C.—M. J. OPPENHEIMER

On the Relationship between Vitamin E, Anterior Pituitary and Adrenal Cortex. B. Bonati, R. Lorenzini, and G. C. Manfredi. *Acta Vitaminol.* 6: 193, 1952.

The plethora of contradictory clinical and experimental data on the action of vitamin E, and the various hypotheses advanced to explain them, led the authors to investigate the relationships between vitamin E and the pituitary-adrenal axis, as reflected in the urinary excretion of 17-ketosteroids and in variations in circulating eosinophile granulocytes. Confusing evidence on the relations between corticotropic hormone, cortisone and cholesterol, and on the relation of vitamin E and cholesterol, suggested the study of the behavior of cholesterol in non-atherosclerotic subjects receiving vitamin E.

Twenty-eight healthy subjects, aged 20–45 years, divided equally as to sex, were studied. One group, whose average daily elimination of 17-ketosteroids and blood cholesterol level had been previously determined, was given intramuscular α-tocopherol acetate (300 mg. per day) for 6 consecutive days, after which the urinary constants and blood chemistry determinations were repeated. A second group, fasted from the previous evening, received 600 mg. of vitamin E by the intramuscular route, after prior determination of the circulating eosinophiles, and 6 hours later the eventual granulocyte variations were evaluated.

The results were substantially negative. Continuous administration of vitamin E did not appreciably modify the urinary elimination of 17-ketosteroids in individuals of either sex. Nor were there, in the same subjects, significant changes in blood cholesterol level, or any correspondence between variations in 17-ketosteroid excretion and in the lipids examined. In the second group of subjects there were no significant variations in circulating eosinophiles after administration of 600 mg. of α-tocopherol acetate.

It would seem on the basis of these results that vitamin E does not directly stimulate adrenal endocrine function or excite pituitary corticotropic activity. The simultaneous absence of variations in urinary 17-ketosteroids, blood cholesterol, and circulating eosinophiles would suggest as much.

Their negative conclusions lead the authors to doubt the efficacy of vitamin E in the large and heterogenous group of diseases which are benefited by treatment with pituitary and adrenal hormones. —C.-J. HOWELL

Specificity of Hemolytic Reaction in Vitamin E-Deficient Erythrocytes. C. S. Rose and P. György. *Am. J. Physiol.* 168: 414, 1952.

Dialuric acid hemolysis of vitamin E-deficient rat red cells *in vitro* is inhibited by a group of fat-soluble antioxidants. These include tocopherols, ethinyl estradiol, diethylstilbestrol, and substituted hydroquinones. Alpha-tocopherols proved to be most effective and were the only ones active *in vivo*.

The ability of hydrogen peroxide to produce hemolysis depends upon vitamin E content of red cells. Catalase opposes dialuric acid hemolysis. The authors consider that the action of dialuric acid depends indirectly on hydrogen peroxide formation during autoxidation. Dialuric acid acts more rapidly and in smaller concentrations than peroxide. It should be pointed out that the effectiveness of alpha-tocopherol resembled its vitamin E effect rather than its antioxidant effect relative to the other tocopherols.—M. J. OPPENHEIMER

Increased Elimination of Sterols Following Injection with Methylnaphthoquinone. L. Arrigo and M. Ravera. *Acta vitaminol.* 6: 101, 1952.

In addition to its role in coagulation of the blood, vitamin K has been shown to increase tissue cholesterol. Studies with radioactive substances have demonstrated the possibility that cholesterol may be utilized by the body for the production of various sterols: hormones, vitamins, bile acids, etc. The adrenals and gonads, in particular, are known to use cholesterol in the elaboration of their hormones, and this utilization is reflected by the appearance in the urine of their specific metabolites: 17-ketosteroids and 11-oxycorticoids. The authors therefore investigated, in albino rats, the urinary elimination of these sterols following stimulation of endogenous cholesterol production by vitamin K administration.

Male rats were kept in metabolic cages for several weeks, during which basal values for daily urinary

elimination of 17-ketosteroids and 11-oxycorticoids, as well as for cholesterol loss in the feces, were established. Fifteen mg./Kg. per day of intramuscular vitamin K (2-methyl-1-4-naphthoquinone in aqueous solution) were then injected, and, after 7 days of treatment, measurements of the same substances were repeated. Following vitamin K administration, 17-ketosteroid and 11-oxycorticoid elimination increased to five times the basal value, and there was a 50 per cent increase in fecal cholesterol.

After examining various possible explanations of these concurrent phenomena, the authors conclude that the increased elimination of these sterols resulted from a direct stimulus excercised by methylnaphthoquinone on the production of specific hormones, rather than representing a nonspecific response to stress. (They note that other stressors, such as vitamin D_2, digitalis, bile salts, etc., may produce hypercholesterolemia without increased elimination of these sterols.)—C.-J. HOWELL

Intravenous Emulsified K_1 in the Treatment of Coumarin-Induced Hypoprothrombinemia. R. Straguell. *Am. Heart J.* 44: 124, 1952.

Emulsified K_1 is a stable, non-toxic emulsion of the fat-soluble vitamin. This substance was employed in doses of 100 mg. intravenously in 7 patients receiving coumarin preparations. Prompt reversal of severe hypoprothrombinemia was noted in each instance. Following the use of I.V. K_1, resistance to the action of coumarins was observed, so that the administration of heparin may be indicated to safeguard the patient in whom further anticoagulant therapy is required. —C. R. SHUMAN

A Radiological Study of the Rate of Passage of Brown and White Bread through the Digestive Tract of Man. R. A. McCance, K. M. Prior, and E. M. Widdowson. *Brit. J. Nutrition* 7: 98, 1953.

The passage of brown and white bread through the alimentary tracts of 6 healthy men and women was studied radiologically by the addition of a small quantity of barium sulfate to the bread. The brown bread appeared to stimulate a greater secretion of saliva or of gastric juice or of both than did the white bread. The brown bread was evacuated from the stomach and passed through the small intestine more rapidly than the white bread. The residue from the brown bread, when in the ileum and in the colon, appeared to be greater than that from the white bread. The residue from the brown bread left the colon 24 hours sooner than that from the white bread.—B. SURE

Influence of Cortisone and ACTH on Appetite. L. M. Van Putten, D. W. Van Bekkum, and A. Querido. *Acta endocrinologica* 12: 159, 1953.

Careful experiments with normal rats showed that ACTH and cortisone in ample doses did not result in a stimulation of appetite. The only effect was a depression of food intake with the higher dosages of cortisone. There was no increase in the spontaneous food intake of normal rats; furthermore, following thermal burns there was no significant stimulation of appetite after ACTH. The authors conclude that it seems likely that the appetite-stimulating effect that has been observed in treated patients must be ascribed to a decrease in the sense of illness or to a general improvement in the patients' condition.—S. O. WAIFE

The Roles of Essential and Non-Essential Amino Acids in Maintaining Liver Xanthine Oxidase. G. Litwack, J. N. Williams, Jr., and C. A. Elvehjem. *J. Biol. Chem.* 201: 261, 1953.

The synthesis of xanthine oxidase has been shown to be sensitive to essential amino acid deficiencies. The authors had previously observed that liver xanthine oxidase activity parallels the growth rate of rats fed diets varying only in the level of protein. The present experiments were designed to determine the relative effects of the individual amino acids.

Using weanling male rats of the Sprague-Dawley strain and a diet in which the amino acids were added in crystalline form for 28-day periods, the importance of the dietary nonessential amino acids for the formation of xanthine oxidase was clearly demonstrated. Nitrogen fed as ammonium citrate or urea exerted a similar effect upon the enzyme formation. The results show that nonessential amino acids, ammonium citrate, or urea, when added isonitrogenously to a purified ration containing 8.0 per cent of the essential amino acids are about equally active in promoting growth in weanling rats.—M. K. HORWITT

Lactose Synthesis in the Mammary Gland Perfused with 1-C^{14}-Glucose. E. Dimant, V. R. Smith, and H. A. Lardy. *J. Biol. Chem.* 201: 85, 1953.

Using a perfusion technique, the mammary gland of a cow was perfused with blood containing 1-C^{14}-glucose. The lactose synthesized under these conditions contained nearly equal amounts of radioactivity in the glucose and the galactose moieties. The C^{14} was located almost exclusively in carbon atom 1 of each of the monosaccharides. It would seem that if glucose is formed in the mammary gland it is formed prior to galactose or that both monosaccharides are formed simultaneously and in equal amounts. This should definitely establish that blood glucose is a precursor of the galactose moiety of milk sugar.

The fat and casein fractions of the milk contained only traces of radioactivity.—M. K. HORWITT

Reactions of Fluoride Ion with Hydroxyapatite. H. G. McCann. *J. Biol. Chem.* 201: 247, 1953.

A problem of long standing in the study of dentin and enamel is the exact nature and structure of the

inorganic material in these tissues. In general, the mineral component of the teeth as well as bone consists chiefly of a basic calcium phosphate which is most probably hydroxyapatite. Chemical methods devised to study the synthetic apatites have been adapted for study of natural tooth substance.

A series of hydroxyapatites were synthesized with a Ca:P mole ratio of 1.593 to 1.667. These apatites were treated in various ways in order to determine the effect of concentration of the fluoride ion, temperature, and Ca:P ratio on the reactions. Concentration of fluoride usually as NaF, was varied from 1 part per million such as occurs naturally in water, up to 2 per cent NaF as used in the topical application of fluoride to the teeth. Temperatures of 20°, 37°, and 100° were employed.

The results indicate that the most important variables in the reaction between fluoride ion and hydroxyapatite are the fluoride concentration and the Ca:P mole ratio of the hydroxyapatite, with the temperature playing a less important role. At 37°, at a concentration of 5 p.p.m. of fluoride, some fluorapatite is formed with all samples of the hydroxyapatite tried. At concentrations of around 0.1 or 0.2 per cent fluoride at 37°, little or no fluorapatite is formed, until the ratio of calcium to phosphorus is over three-fourths of the way between tricalcium phosphate (1.500) and hydroxyapatite (1.667).—M. K. Horwitt